EFFICIENT SYNTHESIS OF NOVEL BODIPY DYES *VIA* C–H FUNCTIONALIZATION

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Samenvatting

Boordipyrromethenen zijn sterk gekleurde vaste stoffen die intens gekleurde oplossingen vormen met een heldere fluorescentie en zijn beter gekend onder de handelsnaam BODIPY. Gedurende de laatste twee decennia zijn deze kleurstoffen een belangrijke klasse van fluoroforen geworden vanwege hun vele uitstekende eigenschappen, zoals blijkt uit de talrijke toepassingen die voor deze kleurstoffen gerapporteerd worden. Specifiek is hun rijke functionaliseringschemie een belangrijke reden voor het belang van deze fluoroforen, omdat dit een vrijwel onbeperkte structurele variatie toelaat en dus toelaat om hun chemische en fysische eigenschappen af te stellen. Spijtig genoeg zijn traditionele functionaliserings-strategieën tamelijk inefficiënt en/of vereisen ze het manipuleren van onstabiele tussenproducten.

Efficiëntere strategieën om derivaten van BODIPY-kleurstoffen te maken zijn gebaseerd op C–H functionalisering. Dit type van reacties maken het invoeren van de gewenste groep in één reactiestap mogelijk. In dit werk werden verschillende C–H functionaliseringsreacties ontdekt en ontwikkeld. Twee verschillende methoden voor het functionaliseren van de C–H binding werden onderzocht. De eerste methode is gebaseerd op transitiemetaalgekatalyseerde C–H activeringsreacties terwijl de tweede strategie gebaseerd is op radicaalreacties.

De eerste reactie die ontwikkeld werd is een palladiumgekatalyseerde C–H arylering bij een hoge temperatuur tussen een boordipyrrometheen en een broomareen. Deze aryleringsreactie vormt 3-monoaryl- en 3,5-diarylkleurstoffen in een matige opbrengst. Een gekruiste C–H dehydroarylering tussen benzothiofeen en BODIPY werd ook onderzocht, maar kon het gewenste product alleen in een lage opbrengst vormen.

Een mildere arylering op kamertemperatuur werd ontwikkeld gebaseerd op de ferroceengekatalyseerde reductie van aryldiazoniumzouten in aanwezigheid van boordipyrrometheenkleurstoffen. Deze radicalaire C–H arylering is een snelle reactie die een grote groep van substituenten kan invoeren in een hoog rendement. Met deze procedure kunnen zowel 3-monoaryl- als 3,5-diarylkleurstoffen gesynthetiseerd worden.

Een tweede radicalaire transformering die ontwikkeld werd gebruikt de oxidatie van organoboranen, zoals kalium trifluorboraatzouten en boronzuren, in de aanwezigheid van een BODIPY-kleurstof en leidt tot een grote groep van 3-monogealkyleerde fluoroforen. Door deze reactie uit te voeren op een hogere temperatuur kunnen ook di-, tri- en tetraalkylkleurstoffen gemaakt worden.

De ontwikkelde reacties zijn krachtige synthetische methoden voor het maken van een grote groep van BODIPY-derivaten. De bruikbaarheid van deze nieuwe reacties werd aangetoond door verschillende geavanceerde moleculen te synthetiseren, waaronder asymmetrisch gesubstitueerde fluoroforen, geannuleerde chromoforen en vaste stof emitterende kleurstoffen.

Summary

Boron dipyrromethenes are strongly colored solids that form intensely colored solutions with bright fluorescence upon irradiation and are better known by their trade name BODIPY. Over the last two decades these dyes have become an important class of fluorophores on account of their many excellent characteristics, as is evident from the numerous applications being reported for these dyes. Particularly their rich functionalization chemistry is a major reason for their attractiveness, as it allows a practically unlimited structural modification and hence provides a method to fine tune their chemical and physical properties. However, the traditional derivatization strategies are rather inefficient and/or require the manipulation of unstable intermediates.

More efficient strategies to functionalize BODIPY dyes are based on C–H functionalization, allowing the introduction of the desired group in one reaction step. In this work, several C–H functionalization reactions were discovered and developed. Two different approaches to achieve functionalization of the C–H bond were explored. The first is based on transition metal catalyzed reactions involving C–H activation, the second strategy is based on radical reactions.

The first developed reaction is a palladium catalyzed C–H arylation between a boron dipyrrin and a bromoarene at high temperatures. This arylation reaction affords 3-monoaryl and 3,5-diaryl dyes in moderate yields. A cross-dehydrogenative C–H arylation procedure between benzothiophene and BODIPY was also investigated, but could provide the desired product only in a low yield.

A milder arylation protocol at room temperature was developed using a ferrocene catalyzed reduction of aryldiazonium salts in the presence of a boron dipyrromethene dye. This radical C–H arylation is a fast and high yielding reaction displaying a broad scope. By using this procedure both 3-monoaryl and 3,5-diaryl dyes can be synthesized.

A second radical transformation that was developed uses oxidation of organoboranes, such as potassium trifluoroborate salts and boronic acids, in the presence of a BODIPY dye and provides a broad range of 3-monoalkylated

fluorophores. By pushing the reaction at a higher temperature di-, tri- and tetraalkylated dyes can also be prepared.

These novel protocols proved to be powerful synthetic tools for the preparation of a broad range of BODIPY derivatives. The utility of these reactions was demonstrated by synthesizing several sophisticated molecules, including asymmetrically substituted fluorophores, annulated chromophores and solid-emissive dyes.

List of abbreviations

AIBN	azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
BODIPY	boron dipyrromethene, 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes
BQ	1,4-benzoquinone
CDI	1,1'-carbonyldiimidazole
cod	1,5-cyclooctadiene
Cp	cyclopentadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CuTC	copper(I) thiophene-2-carboxylate
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridyl
fwhm	full width at half maximum
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
IUPAC	International Union of Pure and Applied Chemistry
IR	infrared
LDA	lithium diisopropylamide
MS	mass spectrometry
MW	microwave
NBS	*N*-bromosuccinimide
NHS	*N*-hydroxysuccinimide
NMR	nuclear magnetic resonance
NXS	*N*-halosuccinimide

ONSH	oxidative nucleophilc substitution of hydrogen
PET	photoinduced electron transfer
PIFA	phenyliodine bis(trifluoroacetate), (bis(trifluoroacetoxy)iodo)benzene
pin	pinacolate
Piv	pivalate, 2,2-dimethylpropanoate
S_NAr	nucleophilic aromatic substitution
TFA	trifluoroacetic acid
TFP	tri(2-furyl) phosphine
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMS	trimethylsilyl
UV-vis	ultra violet-visible light

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General introduction

1. Fluorescent organic dyes

Fluorescent organic molecules are indispensable tools for the study of matter and living systems in material and life sciences, medicine, and (bio)technology. Accordingly, they are used in many applications as the photo-active component.[1] Despite the countless fluorescent molecules that have currently been discovered and the commercial availability of many useful and well-established fluorophores, the ideal fluorescent dye has not yet been found. This ideal fluorophore should combine all the desired chemical and physical characteristics, namely a large molar absorption coefficient, a high quantum yield of fluorescence, a large Stokes shift, an absorption/emission in the red to near infrared region, a high photo- and chemostability, a small size, water solubility, easy tunability of its properties and a facile synthesis. Nonetheless, the search for this ideal fluorophore continues and development of new useful fluorescent molecules remains an active field.

2. Boron dipyrromethenes dyes

2.1. Fundamental properties

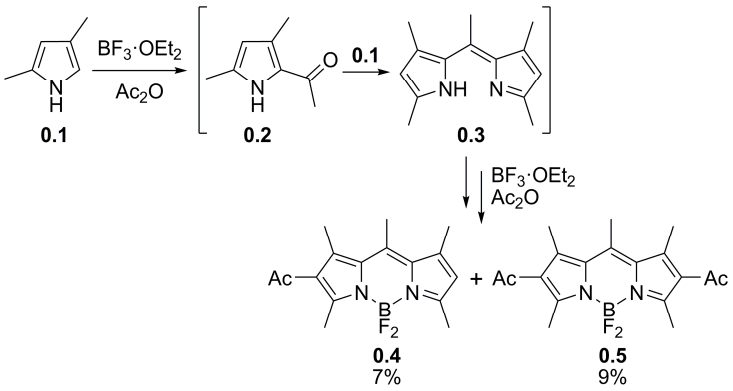
Among the multitude of highly fluorescent dyes available, the boron complexes of dipyrromethenes, or 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes (commonly abbreviated to their brand name BODIPY) have become an increasingly valuable class of fluorophores over the last two decades.[2,3] In general, boron dipyrrins are dyes that strongly absorb light in the visible range, and are often brightly fluorescent due to a combination of a relatively large molar absorption coefficient and a high quantum yield of fluorescence. Their absorption and emission spectra tend to be relatively sharp and are separated by a small Stokes shift. Furthermore, these spectroscopic properties are generally insensitive to the solvent and the pH. The core BODIPY structure itself is uncharged, contributing to the relative low polarity of the molecule. Boron dipyrromethenes also possess low toxicity[4] and excellent thermal[5] and photochemical stability.[6,7] For example, they are stable in the physiological pH-range, only decomposing in strongly acidic and basic conditions.[7] A major

attractiveness of these dyes is undoubtedly their rich functionalization chemistry,[2,8] as this allows a practically unlimited structural modification and hence leads to sophisticated dyes with fine-tuned chemical, optical and (photo)physical properties.[9]

The combination of all these desirable properties is responsible for the strong rise in popularity of BODIPY fluorophores. This popularity is demonstrated by the numerous synthetic and spectroscopic papers being published about these compounds as well as the diverse applications being reported for these dyes. These applications include their use as biological labels[10] and probes,[11] chemosensors,[12] laser dyes,[13,14] photoactive materials in organic photovoltaic devices[13,15] and organic light-emitting devices,[16] potential photosensitizers in photodynamic therapy,[17] and as photocatalysts.[18] Furthermore, several boron dipyrromethene dyes are now commercially available as biological labels,[19,20] probes for bioimaging[19] and laser dyes.[21]

2.2. Discovery and structure

The first BODIPY fluorophores were discovered in 1968 when Treibs and Kreuzer noticed that the acylation of 2,4-dimethylpyrrole **0.1**, with acetic anhydride and boron trifluoride diethyl etherate as a Lewis acid catalyst, resulted in the formation of two highly fluorescent compounds in a low yield, rather than the desired acylated pyrrole **0.2**.[22] These fluorescent compounds arose from an acid catalyzed condensation of pyrroles **0.1** and **0.2** to form the corresponding dipyrromethene **0.3**, followed by complexation with a boron difluoride unit and further acylation resulting in the fluorescent dyes **0.4** and **0.5** (Scheme 0.1).



Scheme 0.1: Discovery of the first BODIPY dyes by Treibs and Kreuzer.

The structure of a BODIPY dye is composed of a complex of a dipyrromethene ligand and a disubstituted electron deficient boron atom, mostly a boron difluoride group. Despite the similarities with dipyrromethenes **0.6**, the numbering and the IUPAC name of this fluorophore **0.7** is not based on that ligand,[23] but on a *s*-indacene molecule **0.8** (Figure 0.1).[2] With the central 8-position of BODIPY often being called the *meso*-position, a terminology originating from porphyrin chemistry. The boron dipyrrin core is formally a zwitterion, however the charge is delocalized over the entire structure. This is evident in the relatively apolar nature of the dye. It is because of this that the structure is usually depicted without formal charges (Figure 0.1).

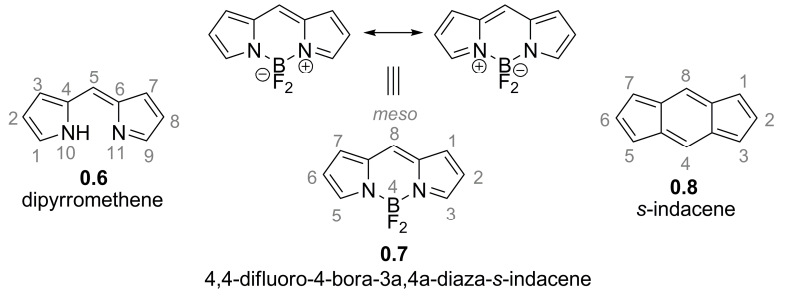


Figure 0.1: Structure and IUPAC numbering of dipyrromethene, BODIPY and *s*-indacene.

Whereas many dipyrromethene based complexes have been reported, only a few are fluorescent (Figure 0.2).[23,24] The quenching of fluorescence in these metal complexes is believed to occur through an electron transfer in the excited state and/or caused by increased intersystem crossing due to the heavy atom effect. Several synthetic strategies have recently been proposed for the preparation of fluorescent dipyrrin based metal complexes with appreciable quantum yields. The Zn(II) species probably represent the most widely investigated type of fluorescent dipyrromethene metal complexes. As an example, zinc complex **0.9** has a fluorescence quantum yield of 0.36 in toluene.[25] The presence of a *meso*-mesityl substituent in this complex is necessary to block non-radiative decay of the excited state through rotation. This is an important and very common strategy to improve the fluorescence quantum yield of dipyrrin complexes to an appreciable level. In contrast, a freely rotating *meso*-phenyl group, instead of a mesityl substituent, results in a very weakly fluorescent metal complex.

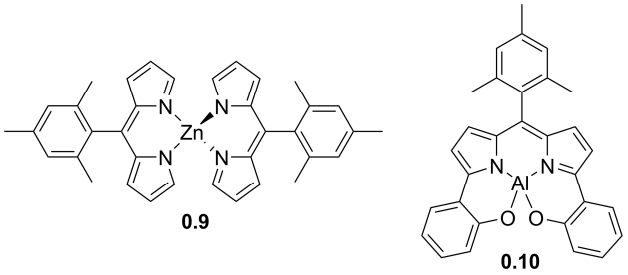


Figure 0.2: Fluorescent dipyrromethene complexes with metals other than boron.

Al(III) dipyrrin complexes are another noteworthy example. Already in the original report of Treibs and Kreuzer, they mentioned the formation of a fluorescent but unstable compound when aluminium(III) chloride was used instead of boron trifluoride as the Lewis acid.[22] Recently, chelation of the aluminium centre with neighbouring phenolate ligands has led to a few stable fluorescent aluminium dipyrrins **0.10**. Again a *meso*-mesityl group was used to limit non-radiative deactivation, resulting in a fluorescence quantum yield of 0.72 in a 99/1 toluene-methanol mixture.[26] This is amongst the highest values for metal dipyrromethene complexes other than BODIPY.

In other words, complexation to boron difluoride is a good strategy to turn a nonfluorescent dipyrrin ligand into a fluorophore by limiting the rotational freedom of the molecule. In fact, BODIPY can be seen as a constrained cyanine dye,[2a,27] improving the fluorescent properties of this well known and widely used polymethine.[28] Using boron difluoride to increase the brightness of the fluorescence of a ligand has been applied in the design of other fluorescent boron complexes (Figure 0.3). In this way a diverse series of fluorophores[29] can be made using N,N-bidentate ligands forming six- (compounds **0.11**,[30,31] **0.12**[30,32] and **0.13**[33]) or five-membered rings (compounds **0.14**[34] and **0.15**[35]), as well as N,O- (compounds **0.16**[36] and **0.17**[37]) and O,O-bidentate ligands (compound **0.18**).[38] The boron complexes of tetrasubstituted azadipyrromethenes **0.11** are very similar to boron dipyrrins, with a nitrogen at the 8-position instead of a carbon, hence they are referred to as aza-BODIPYs. However, these compounds can only be synthesized for heavily substituted azadipyrrins. This limitation, compared to the rich derivatization chemistry of BODIPYs, makes that these aza-analogs **0.11** are overshadowed by their

dipyrromethenes derivatives, despite their larger red-shifts in comparison with the corresponding BODIPY analogs. In fact, of all the known fluorescent boron complexes, boron dipyrrin dyes are by far the most important.

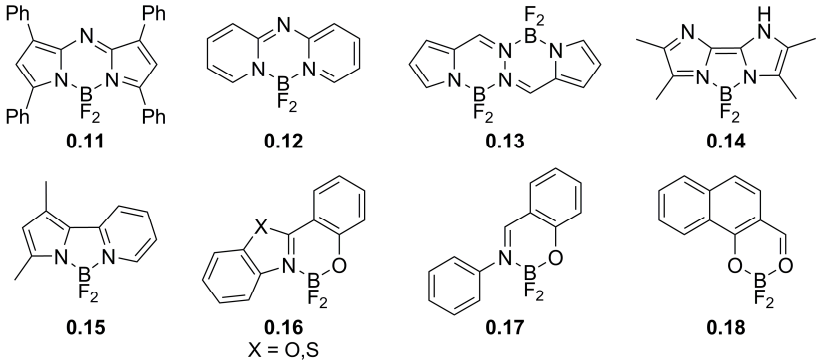


Figure 0.3: Fluorescent boron complexes with ligands other than dipyrromethene.

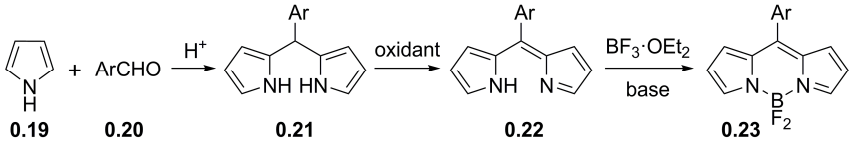
2.3. Synthesis of the BODIPY core

The first synthesis of BODIPY by Treibs and Kreuzer gave the fluorescent product in a low yield due to the presence of an insufficient amount of boron trifluoride etherate and the occurrence of overacylation. However, in the same publication the authors improved their synthesis by first forming and isolating the dipyrromethene and subsequently complexing this ligand with a large excess of boron trifluoride in the presence of an excess of triethylamine as a base.[22]

The first step in the synthesis of the BODIPY core thus begins with the preparation of the corresponding dipyrromethene. There are two distinct synthetic approaches towards this ligand, both adapted from porphyrin chemistry.[23]

The first approach starts with an acid catalyzed condensation of pyrrole **0.19** with an aldehyde **0.20** forming a dipyrromethane **0.21** (Scheme 0.2). Pyrrole is typically used as the solvent in this reaction to prevent polymerization.[39] However, a water based protocol has also been described, avoiding polymerization by precipitation of the formed dipyrromethane **0.21** from the aqueous medium.[40] In this way, a large excess of pyrrole is not needed. Because dipyrromethanes **0.21** are unstable compounds sensitive to light, air and acid, they are best used immediately after preparation. Oxidation of the dipyrromethane **0.21**, with an oxidant like DDQ or the milder *p*-chloranil, yields a dipyrromethene **0.22**. There are only a few examples

where the aldehyde in the first step is not an aromatic aldehyde, as this oxidation tends to fail in other cases.[41] However, a large library of aromatic aldehydes is commercially available, making this approach nonetheless a popular method to introduce functionalities onto the *meso*-position. Subjecting this dipyrrin **0.22** to an excess of base and boron trifluoride etherate affords the desired BODIPY dye **0.23**.[2] It is possible to do all three reactions sequentially, purifying after each step, or a one-pot procedure could be used, by adding the reagents step-wise to the reaction mixture. While the latter is operationally easier, the resulting yields tend to be lower than for the former strategy.

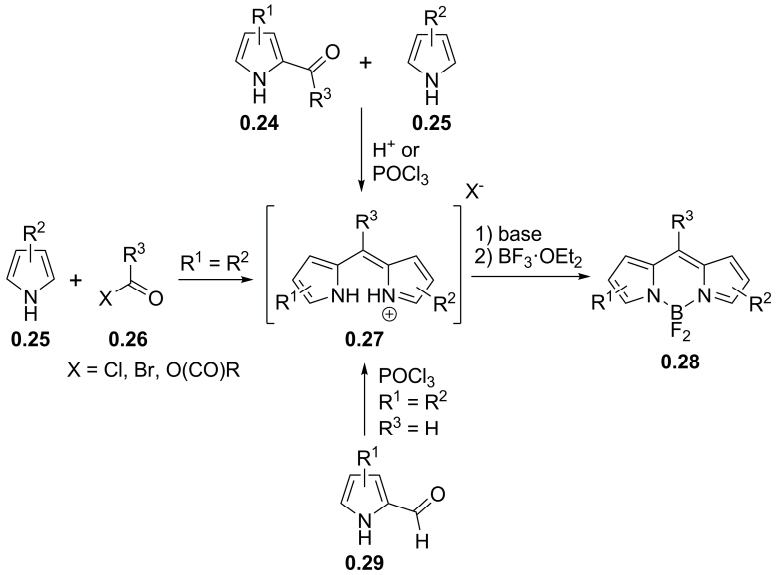


Scheme 0.2: Synthesis of BODIPY *via* an acid catalyzed condensation of pyrrole with an aromatic aldehyde, followed by oxidation and complexation.

The second approach is based on the acid catalyzed condensation of a 2-acylpyrrole **0.24** with a pyrrole **0.25** that is unsubstituted in its 2-position.[23,42] Under these acidic conditions the dipyrrinium salt **0.27** is initially formed. Deprotonation of this salt with base and complexation with boron trifluoride etherate yields a BODIPY dye **0.28** (Scheme 0.3).[2,42] In contrast with the previous procedure, the substituent that ends up at the *meso*-position is not limited to an aryl group, hence a larger range of boron dipyrromethenes can be made using this approach. Furthermore, two different pyrrole moieties can be used in this condensation reaction, making the synthesis of asymmetric boron dipyrrins possible.

A one-step synthesis of symmetric dipyrrinium salts **0.27** is also possible using a similar procedure. In this case, acylation and condensation of a 2-unsubstituted pyrrole **0.25** are done in the same reaction, forming *in situ* a 2-acylpyrrole **0.24** that immediately reacts further to a symmetric dipyrrinium salt **0.27** (Scheme 0.3). The acylating agent in this reaction can be an acid chloride,[43] anhydride[44] or orthoester.[45] An interesting alternative to form symmetrical dipyrrinium salts **0.27** was described by Burgess *et al.*[46] where they discovered that 2-formylpyrrole **0.29** is capable of self-condensation under the influence of phosphorus oxychloride. In both cases, treatment

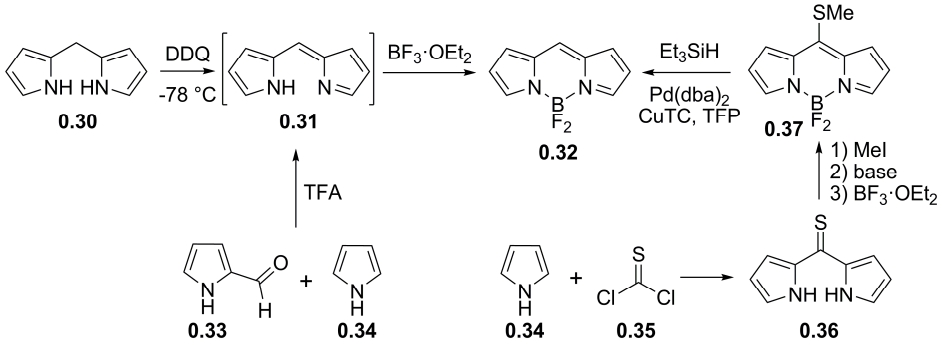
with an excess of base and boron trifluoride etherate yields a BODIPY fluorophore **0.28**.



Scheme 0.3: Acid catalyzed condensation of 2-acylpyrroles and 2-unsubstituted pyrroles to form dipyrrinium salts and BODIPY dyes.

The synthesis of the parent unsubstituted BODIPY system **0.32** would require first the formation of the unsubstituted dipyrrin **0.31**, an unstable compound decomposing at temperatures above -40 °C (Scheme 0.4).[47] Hence, until 2009 there was no synthesis reported for this simple molecule, despite that boron dipyrromethene dyes were discovered more than forty years earlier. Using a trifluoroacetic acid catalyzed condensation of 2-formylpyrrole **0.33** and pyrrole **0.34** followed by complexation with boron trifluoride etherate, allowed the formation of the desired product at room temperature.[48] However, the obtained yield was low. Another way to make the unsubstituted compound **0.32** is *via* oxidation of the corresponding dipyrromethane **0.30**. However, due to the instability of the dipyrrin intermediate the temperature of the reaction medium needs to be kept below -40 °C during the oxidation. Thus oxidation of dipyrromethane **0.30** with DDQ at -78 °C and subsequent complexation in the presence of DBU provides the unsubstituted boron dipyrromethene **0.32** in a low yield of 5-10%.[49] Recently, this procedure has been optimized. Using the milder oxidant *p*-chloranil at -40 °C for a longer time followed by complexation in the

presence of a more sterically hindered amine base provided the unsubstituted boron dipyrrin **0.32** in a good yield of about 70%.[50]



Scheme 0.4: Synthesis of the unsubstituted BODIPY core.

The unsubstituted BODIPY fluorophore **0.32** can also be made in a high yield by reducing a thiomethyl substituted dye **0.37** instead of starting from an unsubstituted dipyrrin **0.31**.[51] The required 8-thiomethyl boron dipyrromethene **0.37** is synthesized in a different way than the two approaches described above. In this case, reaction of pyrrole **0.34** with thiophosgene **0.35** rapidly generates a thioketone **0.36**. By alkylating the sulfur of this compound with methyl iodide a thiomethylated dipyrrinium salts is formed that is converted to the corresponding BODIPY **0.37** with base and boron trifluoride etherate (Scheme 0.4).[52]

3. Synthesis of functionalized BODIPY derivatives

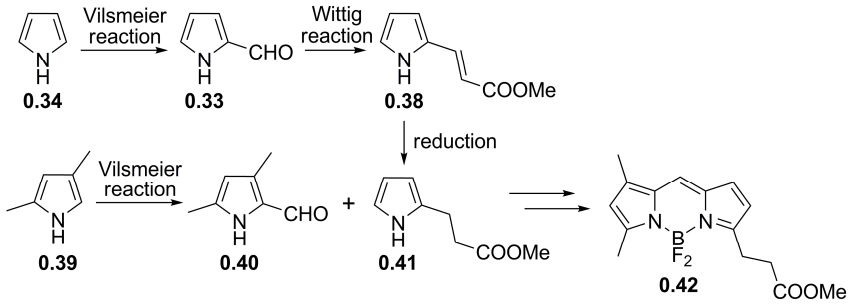
Despite the numerous advantageous properties of BODIPY dyes, there remains nonetheless room for improvement. For example more red-shifted absorption and emission maxima in the far-red and near infrared region are often desirable for many applications.[53] This can be achieved by placing the correct substituents onto the BODIPY core.[8a,9] In fact, the chemical, optical and (photo)physical properties of boron dipyrromethenes can be easily tuned using the rich functionalization chemistry of these dyes.

3.1. From suitably functionalized building blocks

The most straightforward way to prepare functionalized BODIPY dyes is to functionalize their building blocks and use these for the synthesis of boron dipyrromethenes. Although the required synthetic route can be lengthy and low

yielding, this does allow for the introduction of a large variety of substituents and functional groups.

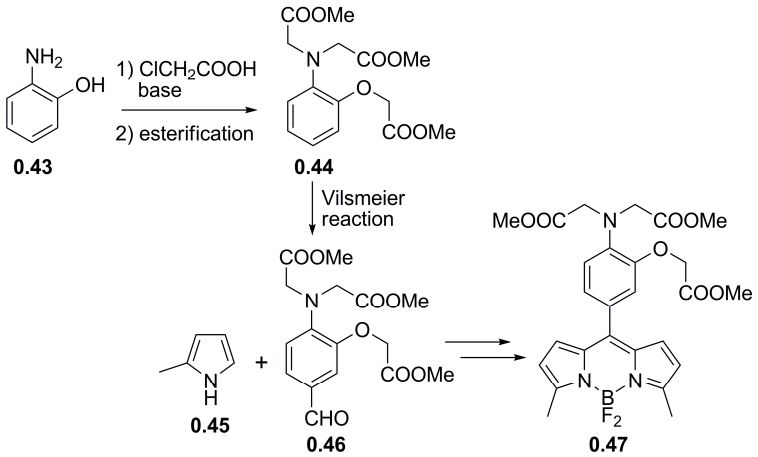
Thus by synthesizing pyrroles with the correct substituents a functionalized dye can be constructed such as the methyl ester of BODIPY® FL **0.42** (Scheme 0.5).[42b,54] This compound is the basis for a commercial labeling fluorophore for amines sold by Life Technologies.[3,19] Its synthesis start from 2-formylpyrrole **0.33** and 2-formyl-3,5-dimethylpyrrole **0.40**, both synthesized *via* a Vilsmeier reaction. 2-Formylpyrrole **0.33** is afterwards converted into a methyl ester **0.41** in two steps. Condensation of this pyrrole with 2-formyl-3,5-dimethylpyrrole **0.40** followed by complexation results in the desired methyl ester BODIPY **0.42**. Saponification of the methyl ester of this dye leads to a carboxylic acid functional group that can be used to label the primary amines of proteins and other amine-containing molecules.



Scheme 0.5: Functionalized pyrroles as building blocks in the synthesis of a BODIPY ester that can be converted into a labeling reagent for amines.

It is also possible to make a functionalized aromatic aldehyde and react this with a pyrrole to make a BODIPY derivative functionalized on its *meso*-position. For example, reaction of 2-aminophenol **0.43** with 2-chloroacetic acid followed by Vilsmeier reaction results in an aromatic aldehyde **0.46**.[55] Acid catalyzed condensation with 2-methylpyrrole **0.45** and oxidation and complexation of the formed dipyrromethane affords an ester BODIPY **0.47** (Scheme 0.6).[56] This methyl ester compound can be saponified to acquire a calcium sensor. The substituent on the *meso*-aryl group of the saponified product can interact with a calcium ion. In the absence of the metal ion, the fluorescence of the sensor is quenched by a photoinduced electron transfer (PET) from the ligand to the BODIPY core. Upon complexation of calcium, this PET process is blocked and fluorescence is restored,

resulting is a large increase in the fluorescence intensity of the sensor in the presence of calcium ions.

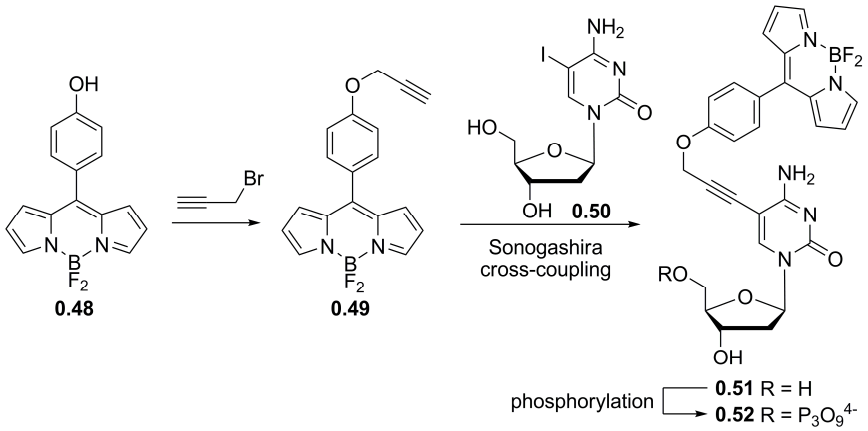


Scheme 0.6: Functionalized aromatic aldehyde as a building block in the synthesis of a BODIPY calcium sensor.

3.2. By reacting BODIPY dyes

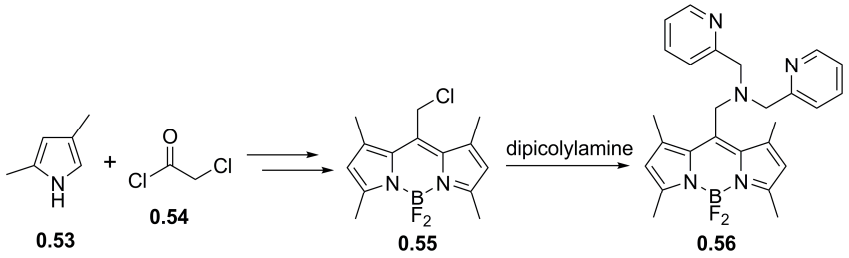
3.2.1. Reaction of peripheral groups

As mentioned previously, the availability of a large library of commercial aromatic aldehydes has made the condensation of a pyrrole with these aldehydes a popular method to introduce simple functionalities onto the *meso*-position. These functional groups are possible synthetic handles to introduce more complex substituents after the synthesis of the BODIPY core. For example, *meso*-phenol boron dipyrrin **0.48** can be functionalized with propargyl bromide, affording a terminal alkyne **0.49** that was further coupled with 5-iodo-2′-deoxycytidine **0.50** using a Sonogashira reaction. This resulted in a BODIPY labeled nucleoside **0.51** that after phosphorylation gave the triphosphate derivative **0.52** (Scheme 0.7).[57] It is possible to incorporate this phosphorylated conjugate **0.52** into DNA without quenching its fluorescence.



Scheme 0.7: Reaction of the *meso*-phenol group to form a BODIPY-nucleoside conjugate.

A reactive *meso*-substituent doesn't have to be introduced *via* an aromatic aldehyde, it can also for instance originate from the condensation of 2,4-dimethylpyrrole **0.53** with chloroacetyl chloride **0.54**. The resulting chloromethyl group of the formed boron dipyrrin dye **0.55** can be substituted with nucleophiles. In this way, a sensor for zinc ions **0.56** can be synthesized (Scheme 0.8).[58] Upon interaction with this metal ion, the fluorescence of the sensor **0.56** is restored by preventing a photoinduced electron transfer, thus visualizing the presence of zinc ions in the medium.

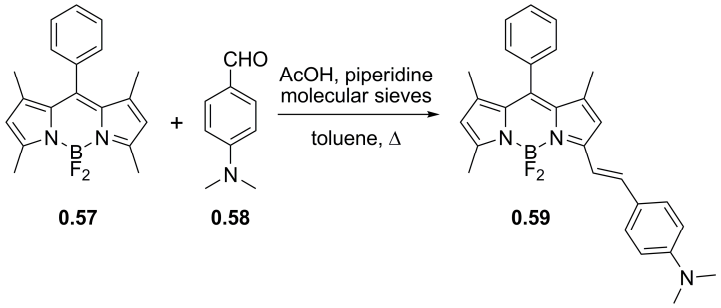


Scheme 0.8: Substitution of a *meso*-chloromethyl group in the synthesis of a BODIPY zinc sensor.

3.2.2. Reaction of the BODIPY core

Similarly to pyridine systems,[59] methyl groups on the BODIPY core are relatively acidic. This acidity allows this dye to be condensed with aromatic aldehydes to form a double bond in a Knoevenagel type reaction. For example, condensation of 1,3,5,7-tetramethyl-BODIPY **0.57** and 4-(dimethylamino)benzaldehyde **0.58** provides a weakly fluorescent styryl dye **0.59** (Scheme 0.9).[60] The low fluorescence quantum

yield of this compound is due to an intramolecular charge transfer originating from the electron-rich 4-(dimethylamino)-phenyl substituent. Protonation blocks the electron pair of the nitrogen donor and hence leads to inhibition of this quenching process. In other words, dimethylamino-BODIPY **0.59** is a pH sensor.

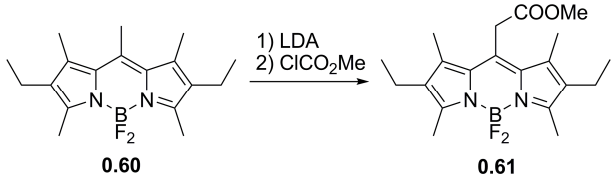


Scheme 0.9: Knoevenagel type condensation of a 3-methyl-BODIPY and an aromatic aldehyde yielding a styryl-BODIPY.

This Knoevenagel type condensation normally takes place under basic conditions or in a buffer, and requires the removal of water from the mixture. This can be done by using molecular sieves or azeotropically by a Dean-Stark apparatus. The facile synthesis of 1,3,5,7-tetramethyl-BODIPYs **0.57** from the condensation of 2,4-dimethylpyrrole **0.53** combined with the ease of these Knoevenagel type reactions have made this approach a popular method for introducing styryl functionalities onto a boron dipyrromethene. Unfortunately, the yields of these reactions are often low. Nonetheless, with this transformation boron dipyrrin dyes can be synthesized with one (3-substituted[60,61] or 8-substituted),[62] two (3,5-disubstituted),[61] three (1,3,5-trisubstituted)[63] or four (1,3,5,7-tetrasubstituted)[63] alkenyl substituents. The 3-methyl group can also react in a similar reaction with a formamide acetal producing a 3-enamine-BODIPY.[64]

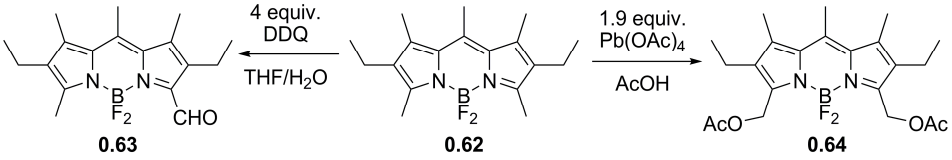
The *meso*-methyl is the most acidic methyl group on the boron dipyrrin core, hence 1,3,5,7,8-pentamethyl-BODIPY **0.60** reacts under these Knoevenagel conditions in the first place on its *meso*-position.[62] Furthermore, it is possible to deprotonate this position with lithium diisopropylamide to lithiate the *meso*-methyl group of highly alkylated dyes. This organolithium compound can then react with a variety of electrophiles, including methyl chloroformate, to form a *meso*-functionalized

fluorophore **0.61** (Scheme 0.10).[65] A similar reaction can take place on the 3-position when the *meso*-methyl is replaced by an aromatic group.



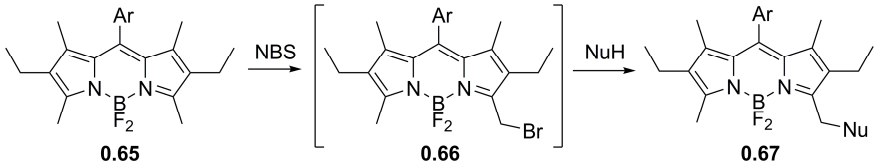
Scheme 0.10: Lithiation and functionalization of a highly alkylated *meso*-methyl-BODIPY.

The 3,5-methyl groups are also oxidizable. Thus, reaction of the heavily substituted dye **0.62** with 4 equivalents of DDQ in aqueous THF leads to the oxidation of a single methyl group to the corresponding aldehyde **0.63**. Similarly, oxidation with lead tetraacetate in acetic acid results in the double ester **0.64** (Scheme 0.11).[66] All pyrrole positions of the starting compound **0.62** have to be substituted otherwise a complex mixture is formed during these reactions. Oxidation of the cyclohexane fused analog of the starting dye leads to the formation of a cyclohexanone derivative.[66a]



Scheme 0.11: Oxidation of the 3,5-methyl substituents of BODIPY.

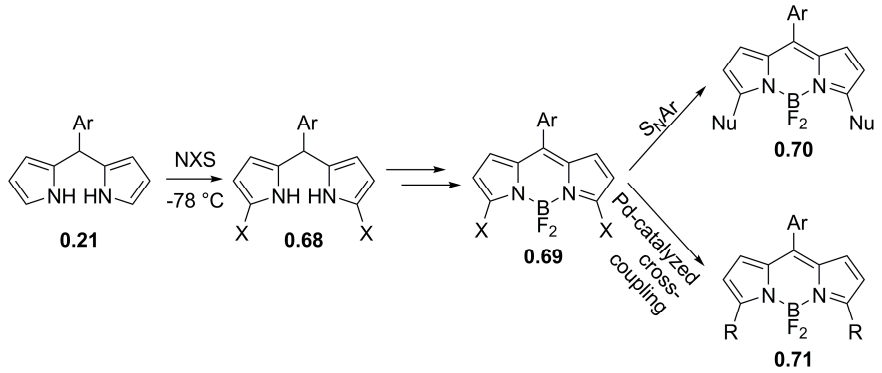
Lastly, bromination of a 3,5-dimethyl-BODIPY **0.65** with NBS results in an unstable compound **0.66** that cannot be isolated. However, addition of a nucleophile to the reaction mixture after the bromination step allows the formation and isolation of the substitution product **0.67** (Scheme 0.12). Using one equivalent of NBS and nucleophile leads to the mono substituted product while two equivalents of both result in the difunctionalized product.[67]



Scheme 0.12: Bromination of the 3,5-methyl substituents of BODIPY followed by nucleophilic substitution.

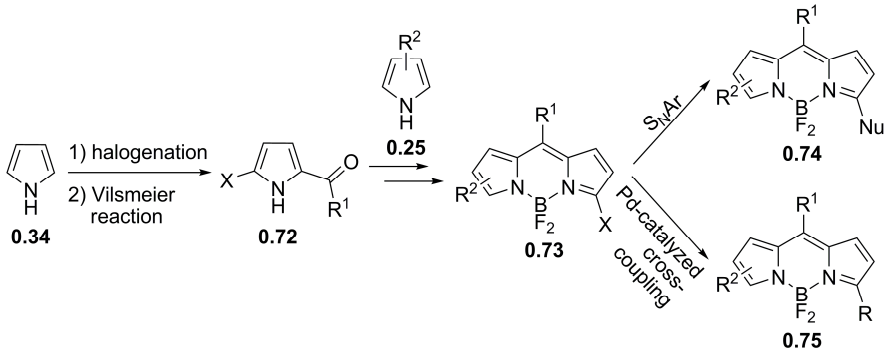
While the use of suitable functionalized pyrrole building blocks and the reactivity of methyl-BODIPY dyes are common methods to synthesize functionalized boron dipyrrins, they both still have major disadvantages. Namely, a laborious pyrrole synthesis and a low total yield for the former and the need for highly substituted dyes combined with quite often a low yield for the latter. In order to find better methods to make functionalized fluorophores, considerable effort has been made in the synthesis of broadly applicable reactive BODIPY dyes. The major advantage of a reactive fluorophore is that the desired functionality can be introduced in the final steps of the synthesis. Thus the first synthetic steps for a broad range of final products are the same and could be done once on a large scale. The most common reactive functional group introduced onto the boron dipyrromethene core is a halogen,[8b] as these could be subjected to the plethora of reactions available for halogenated aromatic heterocycles.

Specifically, 3,5-dihalogenated BODIPYs **0.69** have been extensively used, because they can be easily prepared starting from dipyrromethane precursors **0.21** (Scheme 0.13). Treatment of *meso*-aryl dipyrromethane **0.21** with two equivalents of an appropriate *N*-halosuccinimide in THF at -78 °C gave the corresponding dihalogenated dipyrromethane **0.68** that was subsequently transformed into a BODIPY dye **0.69**. Both chlorination[68] and bromination[69] have been described. 3,5-Diiodinated dyes have also been reported, although they are prepared using a completely different approach.[70] These 3,5-dihalogenated dyes **0.69** can be readily substituted with a broad range of nucleophiles.[71] Conducting the reaction at room temperature leads to a monosubstituted product, while reaction at elevated temperatures with an excess of nucleophile results in the disubstituted product **0.70**. Moreover, these reactive BODIPYs could be subjected to several transition metal catalyzed coupling reactions, such as the Suzuki, Stille, Heck, Sonogashira and Negishi reactions.[72] Again both the mono and disubstituted products **0.71** could be obtained in variable yields.



Scheme 0.13: Synthesis and reactivity of 3,5-dihalogenated BODIPYs made from halogenation of dipyrromethanes.

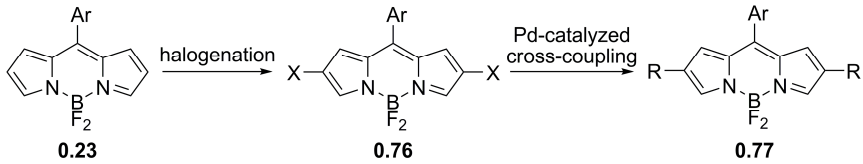
Halogenation of a dipyrromethane **0.21** results in a dihalogenated boron dipyrrin **0.69**. In order to synthesize 3-monohalogenated BODIPYs **0.73**, the starting pyrrole **0.34** is halogenated and acylated resulting in a 5-halogenated acylpyrrole **0.72** that is condensed with another pyrrole moiety **0.25** affording the monohalogenated dye **0.73** after deprotonation and complexation (Scheme 0.14). This reactive fluorophore is, just like its dihalogenated derivative **0.69**, susceptible to nucleophilic aromatic substitution and to palladium catalyzed cross-coupling reactions.[73]



Scheme 0.14: Synthesis and reactivity of 3-monohalogenated BODIPYs made from halogenation of pyrrole.

Perhaps the most widespread method to synthesize halo-BODIPY dyes relies on direct electrophilic halogenation of this fluorophore. The 2,6-positions possess the highest electron density and are susceptible to electrophilic attack. Thus electrophilic halogenation occurs on these positions.[74] Selective mono and dihalogenation can be

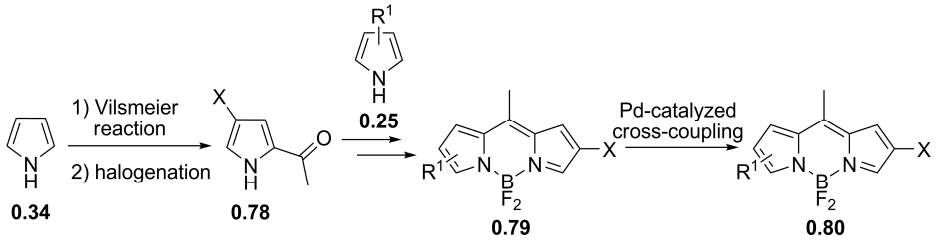
achieved by changing the amount of halogenating agent and the reaction time. Using a large excess of halogenating agent, it is also possible to attack every available pyrrole position of the starting boron dipyrromethene **0.23**.[75] In contrast to these electrophilic halogenation reactions, very recently, a chlorination procedure was described using copper(II) chloride in refluxing acetonitrile that resulted in the formation of 3-mono- and 3,5-dichloro derivatives. Reaction with copper(II) bromide, on the other hand, gave the expected 2-mono- and 2,6-dibromo dyes.[76] 2,6-Halogenated dyes **0.76** can be further functionalized using organometallic cross-coupling reactions to give a variety of derivatives **0.77** (Scheme 0.15).[74] Halogenation at these positions is also a popular method to introduce heavy atoms, bromine and iodine, onto the BODIPY core. The fluorescence of the resulting dye **0.76** is strongly quenched by favouring a spin forbidden transition to a triplet state. This triplet state could then be used to generate singlet oxygen and this is a key step in applications such as photodynamic therapy[17] and photocatalytic oxidation.[18]



0.23 **0.76** **0.77**

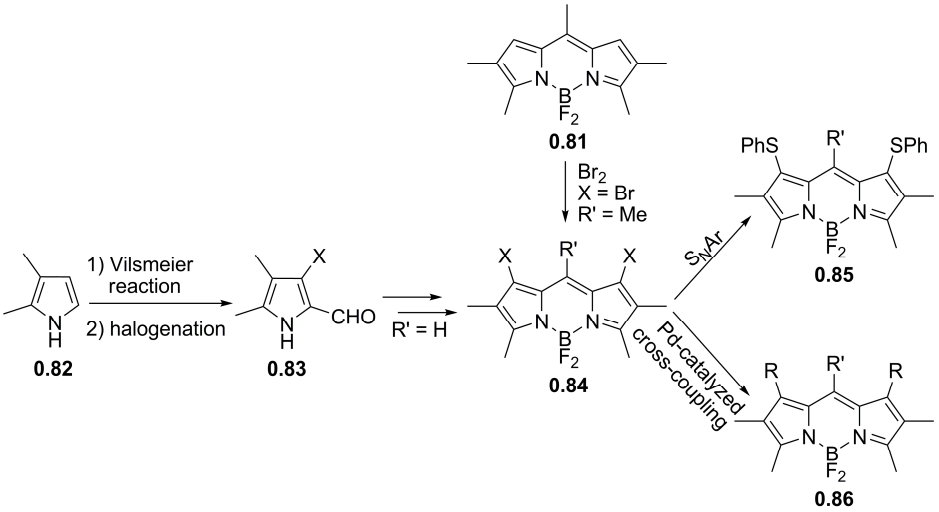
Scheme 0.15: Halogenation of BODIPY followed by functionalization *via* palladium catalyzed cross-coupling reactions.

It is also possible to make a 2-monohalogenated dye **0.79** starting from a halopyrrole **0.78**. In this case, pyrrole **0.34** is first acylated and then halogenated using Oxone® and a sodium halide forming a 4-halogenated acylpyrrole **0.78**. Condensation with a different pyrrole **0.25** followed by deprotonation and complexation afforded the desired 2-halo-BODIPY **0.79** (Scheme 0.16). This reactive dye can be functionalized with transition metal catalyzed cross-coupling reactions.[73]



Scheme 0.16: Synthesis and reactivity of 2-monohalogenated BODIPYs made from halogenation of pyrrole.

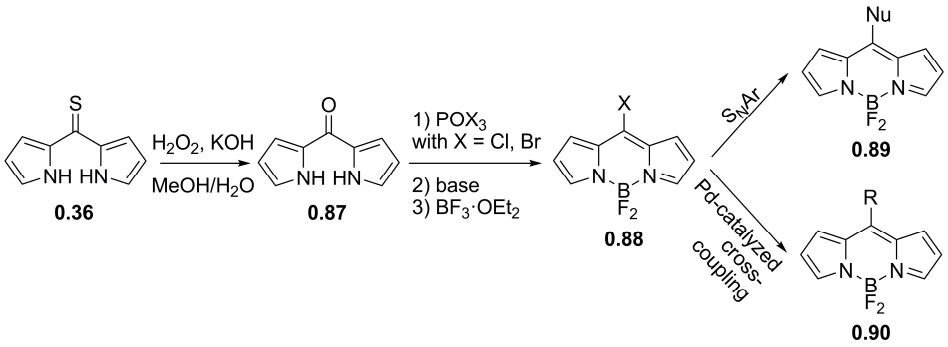
1,7-Dihalogenated BODIPYs **0.84** can be prepared *via* direct halogenation if all other positions are blocked, as in compound **0.81**. Otherwise, halogenation of 2-formyl-4,5-dimethylpyrrole followed by self-condensation under the influence of phosphorus oxychloride results in a similar dye **0.84** (Scheme 0.17). This reactive system can only be substituted with strongly nucleophilic thiolate anions and can be functionalized with palladium catalyzed cross-coupling reactions.[77]



Scheme 0.17: Synthesis and reactivity of 1,7-dihalogenated BODIPYs.

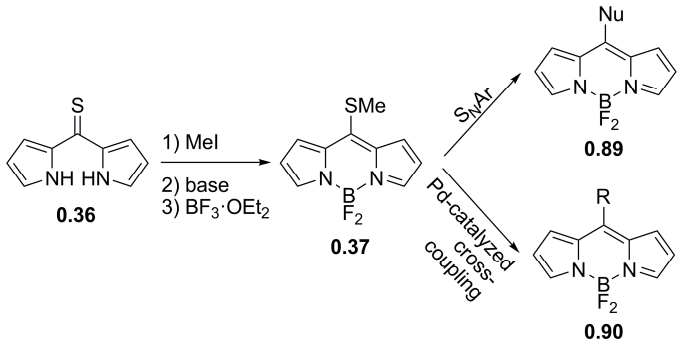
Lastly, a halogen can be introduced onto the *meso*-position by starting from dipyrrylthioketone **0.36**, itself made from pyrrole and thiophosgene. Oxidative conversion of this thioketone provides a dipyrrylketone **0.87** that through deoxygenative substitution with phosphorus oxychloride or phosphorus oxybromide introduces the halogen. Deprotonation of the formed dipyrrinium salts followed by

complexation with boron trifluoride etherate affords a *meso*-chloro or *meso*-bromo BODIPY dye **0.88** (Scheme 0.18). A *meso*-iodinated dye was prepared from the chlorinated derivative by halogen exchange. This 8-halogenated fluorophore is reactive towards nucleophiles and in transition metal catalyzed reactions.[78]



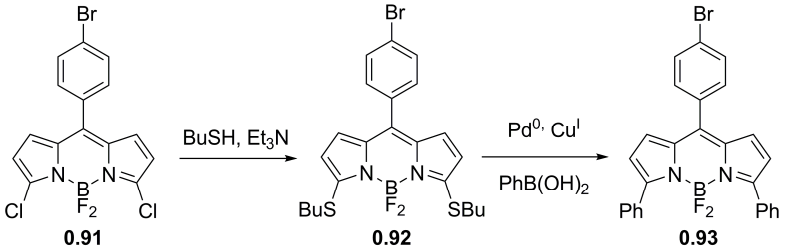
Scheme 0.18: Synthesis and reactivity of *meso*-halogenated BODIPYs.

Dipyrrylthioketone **0.36** can also be used as the starting material for another kind of reactive BODIPY. As described above (section 2.3), alkylation with methyl iodide forms a thiomethylated dipyrrinium salts that can be converted to the corresponding BODIPY dye **0.37** (Scheme 0.19).[52] The thiomethyl group of this fluorophore acts as a pseudohalogen and can be substituted with a variety of nucleophiles.[52,79] However, with some nucleophiles a stochiometric amounts of copper(I) thiophene-2-carboxylate, or another copper(I) salt, is needed to activate the thiomethyl to make it a better leaving group.[80] This copper salt also makes 8-thiomethyl-BODIPY **0.37** reactive in palladium catalyzed Liebeskind-Srogl cross-coupling reactions with aryl and alkenyl boronic acids.[81,82] Organostannanes are also reactive under similar conditions.[82] Lastly as previously mentioned, this *meso*-thiomethyl compound **0.37** can also be reduced to form the unsubstituted BODIPY fluorophore (Scheme 0.4).[51]



Scheme 0.19: Synthesis and reactivity of 8-thiomethyl-BODIPY.

A thioether substituent can also be introduced onto the 3,5-positions by substituting a 3,5-dichloro BODIPY dye **0.91** with butylthiol in basic conditions to yield a 3,5-dithioether dye **0.92** (Scheme 0.20). This compound was subsequently used in a Liebeskind-Srogl reactions providing diaryl-BODIPY **0.93**.[83] An advantage of this method is the orthogonality with other palladium catalyzed cross coupling reactions. Thus the bromine function remains untouched and is available for further functionalization.

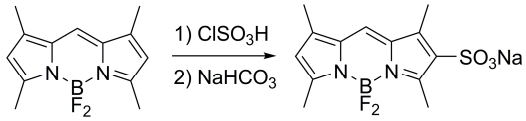


Scheme 0.20: Liebeskind-Srogl reaction of 3,5-dithioalkyl-BODIPY.

Reactive BODIPY dyes have been developed with (pseudo)halogens on any of the available pyrrole positions and they have become important starting materials for the synthesis of functionalized fluorophores. However, their own preparation is often not trivial as it typically requires the synthesis of unstable halogenated pyrroles. Special care is needed during the preparation and handling of these sensitive compounds. In other words, a laborious pyrrole synthesis is not completely avoided. If the desired functionalities could be introduced onto the BODIPY core directly, without the need to make a reactive derivative first, then this problem could be prevented. Thus using the native reactivity of an unfunctionalized boron dipyrromethene it is possible to

place substituents onto this dye in the final steps of the synthesis. By introducing the desired group directly, this synthesis is also more efficient than compared with the approach using a (pseudo)halogenated BODIPY dye.

As mentioned above, the 2,6-positions of boron dipyrrins have the highest electron density making them susceptible to electrophilic substitution such as halogenation (Scheme 0.15). Other electrophilic aromatic substitutions are also possible on these positions. For example, already in the first paper of Treibs and Kreuzer, they mentioned the sulfonation of a simple BODIPY dye **0.94** with chlorosulfonic acid.[22] Unfortunately, the resulting product turned out to be unstable. Another group later discovered that the reaction needs to be quenched with bicarbonate to provide the stable salt **0.95** (Scheme 0.21).[84] This salt is a water soluble fluorophore, which is a useful property in applications such as biological imaging. BODIPY dyes have also been successfully subjected to nitration[85] and Vilsmeier formylation reactions.[86] Most of these reactions were done with dyes substituted on the 3,5-positions **0.94** to avoid regioselectivity issues. In dyes with free 2,6- and 3,5-positions, some of these transformations have been reported to give a mixture of compounds, with both positions being attacked.[87]

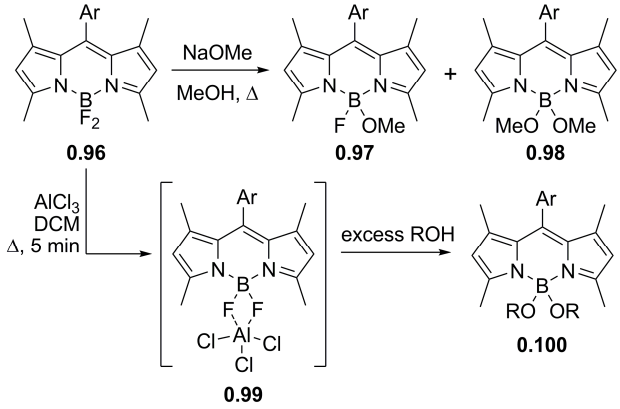


0.94 **0.95**

Scheme 0.21: Sulfonation of BODIPY using chlorosulfonic acid.

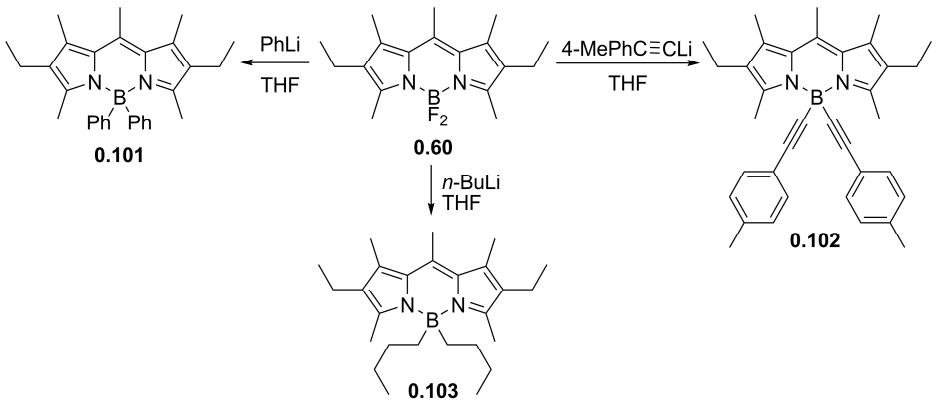
The fluorides of the boron difluoride unit of BODIPY can be substituted with nucleophiles. As the boron centre is a hard Lewis acid, a hard nucleophile is most efficient to displace the fluorides. Thus oxygen nucleophiles can be introduced under basic and Lewis acidic conditions. For instance, refluxing a BF_2-dye **0.96** in basic methanol led to a mixture of monomethoxy **0.97** and dimethoxy products **0.98** (Scheme 0.22).[88] Replacement of the fluorides by methoxy substituents has very little effect on its properties, but it was noted that this substitution increased the water solubility of the resulting dyes.[89] Alternatively, refluxing BODIPY dyes **0.96** in dichloromethane in the presence of a stoichiometric amount of aluminium trichloride presumably activates the fluorine atoms via an intermediate **0.99**, as can be observed

by the rapid disappearance of the starting material. Addition of an excess of alcohol at this stage leads to efficient substitution of the fluorine atoms at room temperature providing exclusively the dialkoxy product **0.100** (Scheme 0.22).[90] Using similar reactions it is also possible to exchange the fluorides with carboxylates.[91]



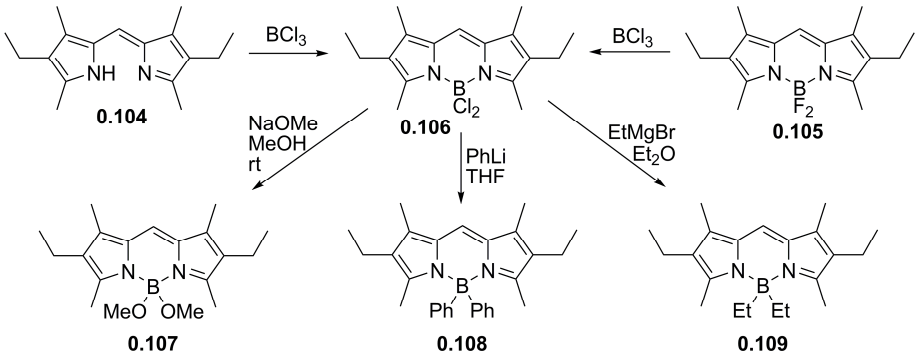
Scheme 0.22: Substitution of BODIPY fluorides with oxygen nucleophiles.

Carbon anions can also attack the boron centre provided that they are hard nucleophiles, as is the case for Grignard and organolithium reagents. In this way, aryl,[92,93] alkynyl[92,94] and alkyl groups[92] can be introduced on the 4-position (Scheme 0.23). The BODIPY substrate **0.60** needs to be highly substituted for this reaction to prevent attack on the pyrrole rings[95] or the *meso*-position[50,96] leading to side products or decomposition. Using a Grignard reagent instead of an organolithium compound can limit this problem and in this way some free positions could be tolerated.[97]



Scheme 0.23: Substitution of BODIPY fluorides with carbon nucleophiles.

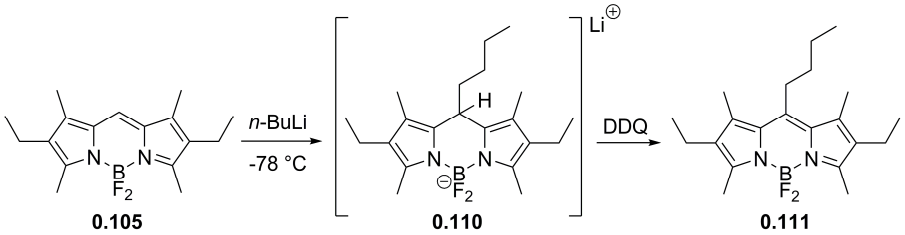
It should be mentioned that a dipyrromethene **0.104** can be complexed with boron trichloride to form the boron dichloride derivative of BODIPY **0.106** (Scheme 0.24).[98] Reaction of dipyrromethene **0.104** with BBr_3 or BI_3 also formed a product, but both resulting compounds were too unstable to be purified and characterized. The weaker bond strength of the B-Cl bonds in 4,4-dichloro-BODIPYs **0.106** make these bonds substantially more labile than the corresponding B-F bonds of 4,4-difluoro-BODIPYs **0.105**. Compared to the traditional boron difluoride dipyrromethenes **0.105**, substitutions at the boron center of 4,4-dichloro-BODIPYs **0.106** proceed under milder conditions and require shorter reaction times. For example, substitution of the chlorides with sodium methoxide occurs at room temperature (Scheme 0.24), while this reaction for the corresponding difluoride dye **0.96** requires heating (Scheme 0.22). Carbon nucleophiles can also easily substitute the chlorides of these 4,4-dichloro-BODIPYs **0.106**. Other than by complexation of a dipyrromethene **0.104** it is possible to make this more reactive dye **0.106** starting from a 4,4-difluoro-BODIPY **0.105** by reacting this difluoride dye with boron trichloride.[50,99] The resulting boron dichloride fluorophore **0.106** can react *in situ* with a nucleophile to form the desired substituted product. In this way, purification of the labile 4,4-dichloro-BODIPY intermediate **0.106** is avoided.



Scheme 0.24: Synthesis of a boron dichloride dipyrromethene and substitution of the chlorides.

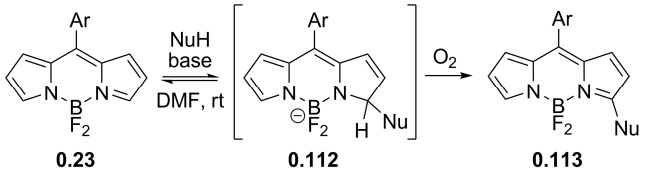
As mentioned previously, reaction of an organolithium reagent with a *meso*-unsubstituted BODIPY **0.105** can result in an attack on this free position by the organometal compound. Thus reaction with butyllithium initially formed a charged dipyrromethane-type intermediate **0.110**. This transformation was done at -78 °C in

order to limit substitution of the fluorides at the boron atom. The unstable intermediate **0.110** can be converted into a *meso*-butyl boron dipyrrin dye **0.111** by oxidation at room temperature (Scheme 0.25).[96] Less alkylated BODIPYs gave a lower yield for this reaction, presumably due to a lower stability of the intermediate **0.110**. A similar reaction with phenyllithium resulted in a mixture of compounds because this organolithium reagent attacks both the *meso*- and 4-positions.



Scheme 0.25: *Meso*-butylation of a *meso*-unsubstituted BODIPY with butyllithium.

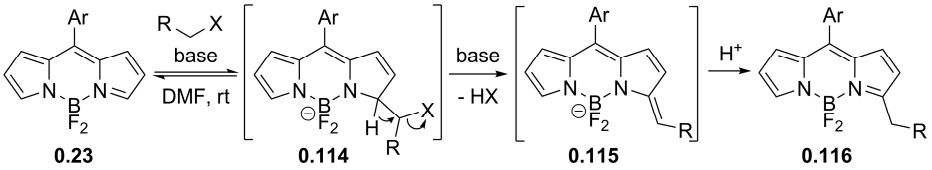
Soft nucleophiles are capable of reacting at the 3-position of a *meso*-aryl BODIPY dye **0.23** without reacting at the 4-position, thus forming a σ^H-adduct **0.112**, as is the case with many electron poor aromatic systems. Because a hydride is a poor leaving group this adduct will normally dissociate to the starting materials in order to restore the aromaticity. However, oxidation of the σ^H-adduct **0.112** with an external oxidant can also re-establish said aromaticity resulting in a substituted product **0.113**. This process is called an oxidative nucleophilic substitution of hydrogen (ONSH).[100] In the case of a boron dipyrromethene **0.23**, reaction at room temperature in DMF in the presence of oxygen as the oxidant allows the direct introduction of aliphatic amines and enolates (Scheme 0.26).[101] The previous mentioned reaction between *meso*-unsubstituted BODIPY **0.105** and butyllithium can also be seen as an oxidative nucleophilic substitution of hydrogen.



Scheme 0.26: Oxidative nucleophilic substitution of hydrogen on BODIPY dyes.

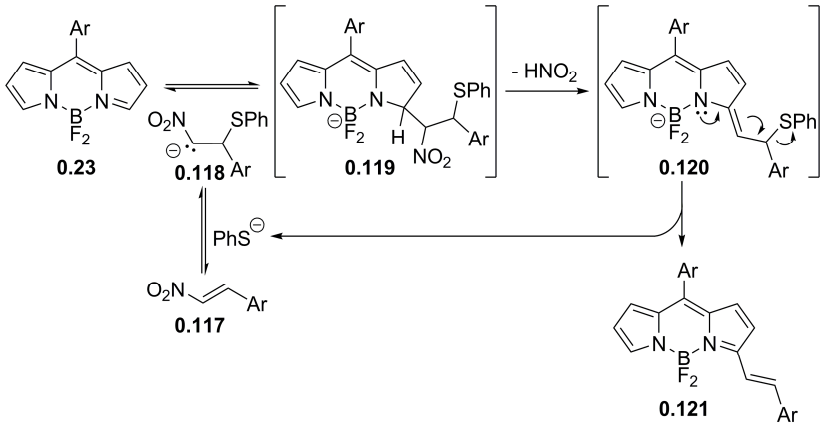
Another way to transform the σ^H-adduct **0.114** into an aromatic product occurs in the vicarious nucleophilic substitution of hydrogen.[100] In this case, the reacting

nucleophile contains a leaving group X at the nucleophilic center. The σ^H-adduct **0.114** formed *via* addition of such a nucleophile undergoes a base-induced β-elimination of HX affording an intermediate **0.115** that after protonation rearomatizes to the substitution product **0.116**. With a sufficiently strong base this is possible between BODIPY dyes **0.23** and enolates bearing a leaving group on the α-carbon without needing an oxidant (Scheme 0.27).[102] The leaving group on the enolate can be varied, allowing even a thioether to take this role.



Scheme 0.27: Vicarious nucleophilc substitution of hydrogen on BODIPY dyes.

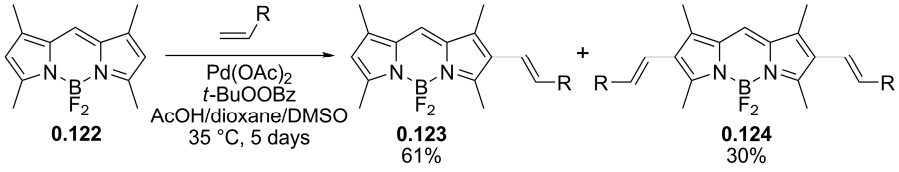
A thioether as leaving group in the vicarious nucleophilic substitution of hydrogen is exploited in a tandem reaction directly providing a styryl-BODIPY **0.121** from an unsubstituted dye **0.23** and a nitrostyrene **0.117** (Scheme 0.28).[102] This nitrostyrene is readily available from the Henry reaction between nitromethane and an aromatic aldehyde.[103] The first step of this tandem reaction is a reversible nucleophilic Michael type addition of the thiophenolate catalyst on nitrostyrene **0.117** forming a stabilized nitronate anion **0.118**. This is followed by the vicarious nucleophilic substitution of BODIPY **0.23** with this anion **0.118**. Elimination of nitrous acid from the formed σ^H-adduct **0.119** under the influence of base and subsequent rearomatization through a retro-Michael addition provides the styrylated product **0.121** and recovers the thiophenolate catalyst. This tandem reaction is selective for monostyrylation, and in most cases, the disubstituted product was only observed in trace amounts. All attempts to push this reaction to disubstitution were unsuccessful.



Scheme 0.28: Tandem reaction between BODIPY and nitrostyrene using a thiophenolate catalyst.

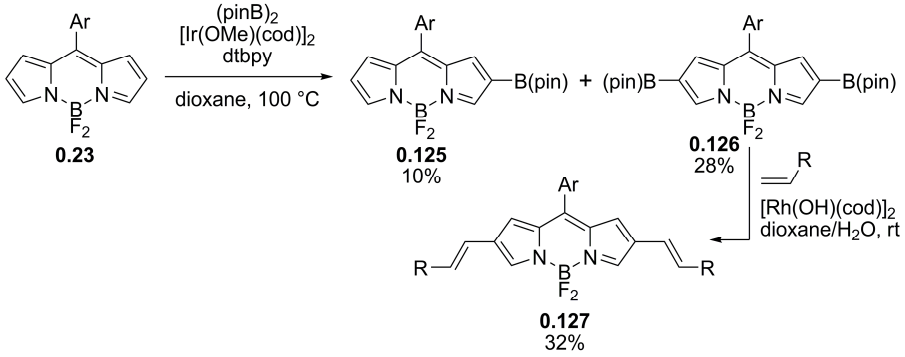
Recently, a lot of attention has gone to direct, transition metal catalyzed C–H functionalization. During the last two decades, these atom economical reactions have become an increasingly attractive alternative to traditional cross-coupling reactions. Thanks to the advancements in this area, heteroaromatic systems can now be easily and efficiently functionalised using direct arylations,[104] alkynylations,[105] alkenylations,[106] alkylations,[107] halogenations,[108] carbonylations,[109] *etc.*[110] Similar protocols can be applied to BODIPY dyes, although examples are currently still limited.

The first published example is the palladium catalyzed C–H alkenylation at the 2,6-positions of a boron dipyrromethene dye, as reported by Burgess *et al.*[111] In this reaction, C–H activation of a tetramethyl-BODIPY **0.122** coupled with Heck type alkenylation leads to mixture of mono- **0.123** and difunctionalized **0.124** products in moderate to good yield after 5 days (Scheme 0.29). In order to be able to use palladium in catalytic amounts, a stoichiometric oxidant is needed to regenerate the catalyst. The presence of an oxidant combined with the acidic solvent and long reaction times could make this reaction incompatible with more sensitive substrates.



Scheme 0.29: Direct oxidative C-H alkenylation of tetramethyl-BODIPY (R = COOMe).

Another way to alkenylate on this position was described by the group of Osuka.[112] They developed an iridium catalyzed C–H borylation on the 2,6-positions of BODIPY **0.23**. Thus using bis(pinacolato)diboron a mixture of mono- **0.125** and diborylated **0.126** products were formed in a low to moderate yield (Scheme 0.30). A rhodium catalyzed Heck reaction of the diborylated BODIPY fluorophore **0.126** can subsequently provide the alkenylated derivative **0.127**. Unfortunately, the borylated products are not stable enough for easy purification by column chromatography on silica gel. To eliminate tedious separation and decomposition of the products on silica gel, the Heck reaction can be done using the mixture of the previous reaction without purifying the borylated intermediates.



Scheme 0.30: Iridium catalyzed direct borylation followed by a rhodium catalyzed Heck-type addition (Ar = mesityl, R = $COOC_6H_{13}$).

4. Influence of structural factors on the optical properties

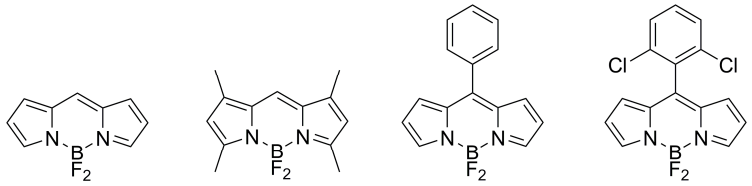
A typical BODIPY dye **0.32** absorbs and emits green light around 500 nm and is brightly fluorescent due to a combination of a relatively large molar absorption coefficient and a high quantum yield of fluorescence. The absorption and emission spectra are mostly insensitive to the solvent, tend to be relatively sharp and are separated by a small Stokes shift.[2,3]

Using the rich functionalization chemistry of BODIPY dyes (section 3) it is possible to tune these spectroscopic properties by introducing the correct substituents on the appropriate positions of the core structure. In this way, derivatives can be synthesized that cover the entire visible spectral range.[9] It is not always

straightforward to predict the effect of different substituents on the photophysical properties, but some trends can be observed.

Substituting boron dipyrrin dyes generally leads to an enhanced stability of the fluorophore. In general, introduction of alkyl groups has no significant effect on the spectroscopic properties. Just like the unsubstituted system **0.32**, alkylated dyes **0.94** are highly fluorescent compounds absorbing and emitting in the green spectral region (Figure 0.4).

Most boron dipyrromethenes contain an aryl group on their *meso*-position, as a result of the used BODIPY synthesis (section 2.3). There is very little conjugation between this aryl substituent and the fluorescent core as both groups are nearly perpendicular to each other to minimize sterical interactions. Hence, *meso*-arylated dyes **0.128** are not red-shifted compared to the unsubstituted system **0.32** (Figure 0.4). However, there is an effect on their quantum yield of fluorescence. *Meso*-arylated dyes **0.128** generally have a low value for this parameter and this has been attributed to fast rotation of the aryl group allowing a non-radiative decay of the excited state.[113] Restricting this rotation by placing substituents on the *ortho*-positions of the aryl group leads to an improved quantum yield of fluorescence, as is the case for *meso*-mesityl and *meso*-(2,6-dichlorophenyl) dyes **0.129**. Placing substituents at the 1,7-positions of BODIPY also hinders the rotation of the 8-aryl group and thus has a similar effect.



0.32
λ_{abs}: 499 nm
λ_{em}: 535 nm
Φ_f: 0.93

0.94
λ_{abs}: 505 nm
λ_{em}: 516 nm
Φ_f: 0.80

0.128
λ_{abs}: 499 nm
λ_{em}: 514 nm
Φ_f: 0.025

0.129
λ_{abs}: 509 nm
λ_{em}: 522 nm
Φ_f: 0.80

Figure 0.4: Spectroscopic properties of a few basic BODIPYs in ethanol (**0.32**,[51] **0.94**[4b] and **0.128**[114]) and methanol (**0.129**).[115]

Organic chromophores possessing strong absorption and fluorescence bands in the far-red and near infrared region are highly desired for many applications.[53] Unfortunately, the absorption and emission maxima of BODIPY dyes are located

around shorter wavelengths. To make these dyes more broadly applicable it is useful to create derivatives with a more red-shifted spectrum. Increasing the length of the conjugation in the structure is the most used method to introduce a bathochromic shift in the spectra of boron dipyrrins (Figure 0.5). This is conveniently achieved by placing aryl groups on the system, as in compound **0.130**. Further extension of the conjugation, with larger aromatic systems or by connecting the chromophore core and the aryl group with double (in **0.131**) or triple bonds (in **0.132**), shifts the absorption and emission maxima of the resulting dyes even further to the red.

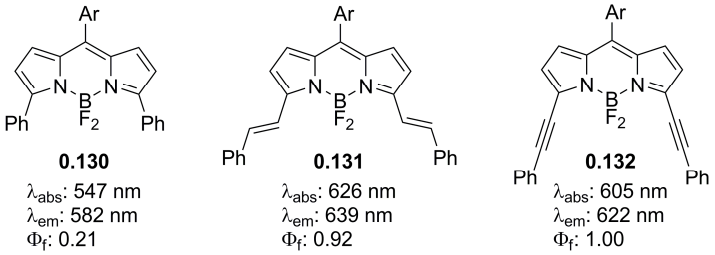
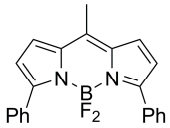
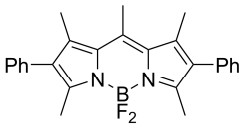


Figure 0.5: Effect of a longer conjugation on the spectroscopic properties of BODIPY in methanol (Ar = *p*-tolyl).[72a]

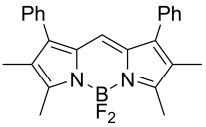
The position where the conjugating groups are attached influences the extent of the achieved red-shift (Figure 0.6). Aryl groups connected to the 3,5-positions (in **0.133**) are located at the ends of the conjugation path of the BODIPY core and hence result in the greatest bathochromic shift. In other words, substituting these positions is the most effective way to increase the conjugation length. A dye with the same groups at the 2,6-positions **0.134** emits at a shorter wavelength. Extending the conjugation at the 2,6-positions also increases the Stokes shift of the fluorophore. Aryl groups placed on the 1,7-positions (in **0.135**) provide an even smaller red-shift, while arylation on the 8-position (in **0.128**) has only a small to negligible effect on the absorption and emission maxima.



0.133
λ_{abs}: 544 nm
λ_{em}: 577 nm
Φ_f: 0.64



0.134
λ_{abs}: 519 nm
λ_{em}: 559 nm
Φ_f: 0.43



0.135
λ_{abs}: 538 nm
λ_{em}: 549 nm
Φ_f: 0.94

Figure 0.6: Effect of the position of the extended conjugation on the spectroscopic properties of BODIPY in DCM (**0.133**),[116] ethanol (**0.134**)[43b] and methanol (**0.135**).[77]

Substituting the BODIPY core with heteroatoms also influences the spectroscopic properties of the resulting dyes. However, the effect of heteroatoms on the spectral maxima is less straightforward than for arylation as both bathochromic and hypsochromic shifts are possible depending on the heteroatom and its position on the BODIPY core. For example, placing an amino group on the 3-position introduces a red-shift[71a,73b] while placing the same substituent on the 8-position results in a blue-shift in both the absorption and emission maxima.[78a,79a-c,117]

As such, knowledge of these structural traits can help to identify the target BODIPY compound for a specific application. For example, highly desirable dyes combining red-shifted absorption and emission maxima with a high quantum yield of fluorescence will most likely have an extended conjugation located at the 3,5-positions, and lack a rotating *meso*-aryl group.

5. Conclusion

BODIPY dyes have come a long way from their initial discovery in 1968, and are now well established as versatile fluorophores. The growing importance of these boron complexes is evident in the numerous applications being reported for these dyes. The main attractiveness of BODIPY fluorophores is their bright fluorescence together with their rich functionalization chemistry. This rich chemistry is appealing as it allows the synthesis of sophisticated dyes with fine-tuned chemical, optical and (photo)physical properties.

A typical functionalization strategy starts from suitably functionalized pyrroles or uses reactive BODIPY dyes, such as halogenated compounds or derivatives containing a thioether as a pseudohalogen. While these two methodologies are well documented they tend to suffer from the use of unstable intermediates and/or the need

for a long synthetic route. These two disadvantages can be avoided by introducing functional groups more efficiently onto the BODIPY core, for example by using C–H functionalization reactions, allowing the synthesis of new fluorophores in a single atom economical step. In the last few years, a handful of limited examples of such direct derivation reactions for boron dipyrrins have been described. However, many types of direct functionalization reactions of these dyes remain largely unexplored. In order to make C–H functionalization competitive with the versatility of reactive BODIPY dyes and thus a superior strategy, new and more powerful protocols need to be developed.

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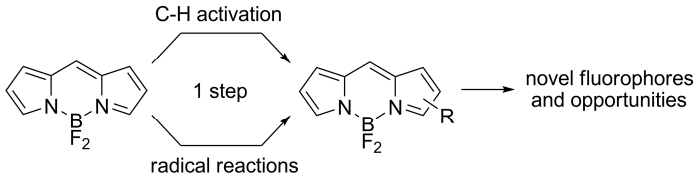
Goals and objectives

The main goal of this PhD project is the development of new C–H functionalization protocols for BODIPY dyes allowing the synthesis of novel fluorophores in a single atom economical step (Scheme 0.31). These efficient derivatization strategies would be a valuable addition to the functionalization chemistry of boron dipyrrins as they provide extra alternatives to make new and sophisticated chromophores while avoiding the tedious synthesis of substituted pyrrole building blocks as well as preventing unstable intermediates.



Scheme 0.31: Efficient synthesis of novel BODIPY dyes in one synthetic step using C–H activation or radical reactions.

Two different approaches to achieve functionalization of the C–H bond will be explored. The first is based on transition metal catalyzed reactions involving C–H activation, for which only two reactions have been reported so far for the BODIPY system. Namely, a C–H alkenylation and a C–H borylation on the 2,6-positions (General introduction, section 3.2.2). Other reactions based on C–H activation will be investigated, such as C–H arylation, and the reactivity of the other positions of the fluorophore core towards these reactions will be examined.

The second strategy to functionalize in one synthetic step is based on radical reactions. Currently, there are no practical examples known of radical reactions on BODIPY dyes, despite the versatility of this type of transformations as well as their mild reaction conditions. Hence, the feasibility of radical functionalization of boron dipyrromethenes will be explored.

Using both transition metal catalyzed C–H functionalization and radical C–H functionalization new protocols compatible with BODIPY dyes will be developed. Afterwards, the optimal reaction conditions will be used to explore the scope of these new transformations. The selectivity of the developed reactions will also be investigated. Particularly desirable is substitution of the 3,5-hydrogens due to the

largest effect of a longer conjugation at these positions (General introduction, section 4). Finally, the novel opportunities provided by the newly developed procedures will be investigated, such as the synthesis of sophisticated fluorophores with unique properties that are unavailable using the current functionalization strategies of BODIPY.

The development of these new transformations will provide a great variety of new fluorophores with a range of substituents on different positions of the BODIPY core. This presents an opportunity to investigate the relationship between the structure and the spectroscopic properties of these dyes. Although this is not the main goal of this project, the spectroscopic properties of the new boron dipyrrins that will be formed during the development of new C–H functionalization reactions will be measured to gain an insight into this relationship.

Chapter 1. Direct palladium catalyzed C–H arylation of BODIPY dyes

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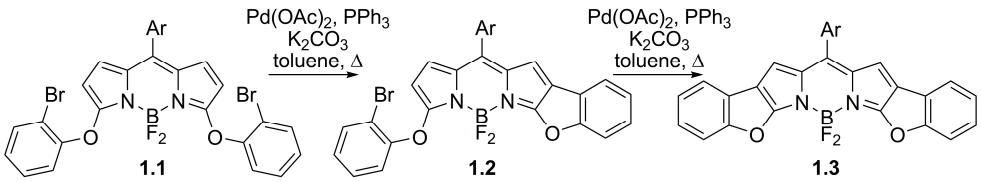
L. Wang, **B. Verbelen**, C. Tonnelé, D. Beljonne, R. Lazzaroni, V. Leen, W. Dehaen, N. Boens, *Photochem. Photobiol. Sci.* **2013**, *12*, 835–847.

1. Introduction

Of the different substituted BODIPY dyes, those that posses an extended conjugation are of particular interest. This is because they display electronic spectra that are red-shifted relative to an unsubstituted BODIPY fluorophore. One excellent way to achieve a bathochromic shift is to introduce aryl groups on the 3,5-positions (General introduction, section 4). Such dyes can be synthesized starting from 2-arylated pyrroles.[1] However, the synthesis of these pyrroles and their subsequent conversion to boron dipyrrins is a long multi-step synthesis with a low overall yield. Another traditional method to prepare arylated fluorophores is via Suzuki or Stille coupling of organometallic compounds with 3-halo- or 3,5-dihalo-BODIPYs.[2] Unfortunately, the synthesis of such halogenated dyes requires unstable 2-halopyrroles or 1,9-dihalogenated dipyrromethanes and hence multiple steps are still required in order to access the desired arylated dyes.

A more efficient method to arylate molecules uses transition metal catalyzed C–H functionalization. Such a direct C–H arylation would be an interesting alternative strategy to substitute the BODIPY core and in this way create fluorophores with red-shifted electronic spectra. Previously, our group successfully used an intramolecular C–H arylation to synthesize an annulated BODIPY dye **1.3** (Scheme 1.1),[3] illustrating that such direct transformations are indeed possible for boron dipyrrins. Given the potential of C–H functionalization, we set out to fully investigate the feasibility of direct intermolecular palladium catalyzed C–H arylation on readily available *meso*-substituted BODIPY dyes **1.4** *via* reaction with arylhalides.

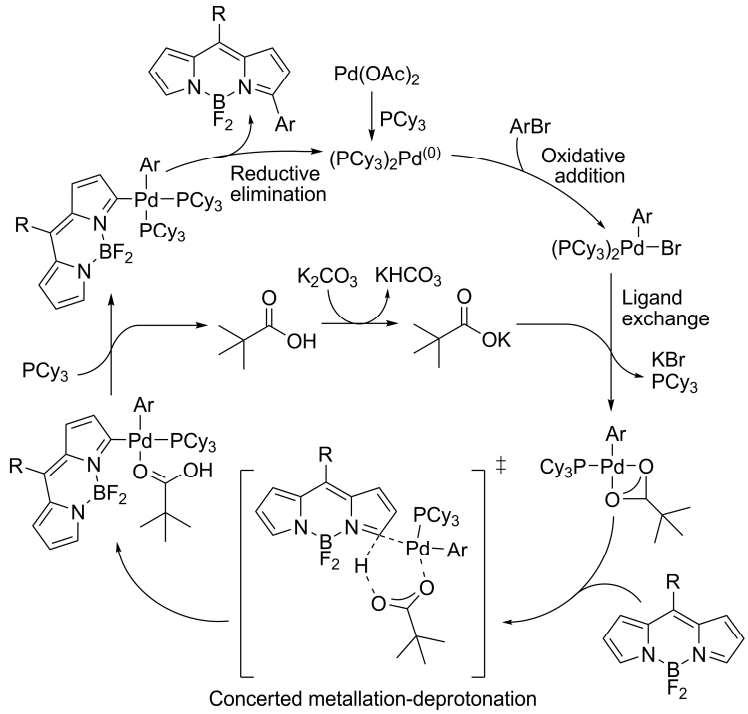


Scheme 1.1: Synthesis of an annulated dye using an intramolecular C–H arylation (Ar = *p*-tolyl).

2. Optimization of the reaction

The conditions previously optimized by our group for intramolecular direct arylation of BODIPY,[3] were used to test an intermolecular C–H arylation of a boron dipyrromethene with a bromoarene. Thus *meso*-2,6-dichlorophenyl-BODIPY **1.4** and bromobenzene were refluxed in toluene in the presence of potassium carbonate, palladium(II) acetate and triphenylphosphine. The *meso*-2,6-dichlorophenyl dye **1.4** was chosen as the starting material because it can easily be synthesized in a semi-large scale and has a high quantum yield of fluorescence (General introduction, section 4). To our delight, the desired phenyl-BODIPY **1.5** was indeed formed after 48 hours, although in a low yield (Table 1.1, entry 2). Due to the slow reaction rate of this initial experiment the majority of the starting material was recovered.

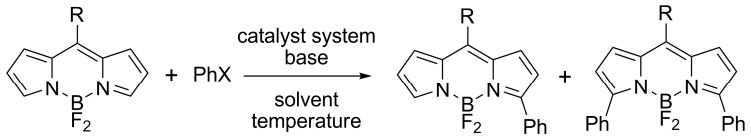
Characterization of the formed product **1.5** showed that bromobenzene had reacted exclusively at the electrophilic 3-position. Therefore, the most likely mechanism for this C–H activation is a concerted metallation-deprotonation involving carbonate as an intramolecular base (Scheme 1.2).[4] In contrast, with an electrophilic palladation mechanism substitution of the nucleophilic 2-position of BODIPY would be expected instead. Since pivalate (*i.e.* 2,2-dimethylpropanoate) is known to accelerate C–H functionalization proceeding *via* a concerted metallation-deprotonation mechanism,[5] addition of a substoichiometric amount of pivalic acid (PivOH, *i.e.* 2,2-dimethylpropanoic acid) to the reaction mixture was tested. As expected, this increased the reaction rate of the C–H arylation. The estimated *in situ* yield determined *via* NMR spectroscopy increased from 4% after 4 days without pivalic acid (Table 1.1, entry 2) to 17% with this additive (Table 1.1, entry 6).



Scheme 1.2: Proposed catalytic cycle for direct C–H arylation of BODIPY based on a concerted metallation-deprotonation mechanism.

However, further improvement was needed and hence, other reaction conditions were tried. By changing the phosphine ligand with more electron rich or bidentate ligands (Table 1.1, entries 7-9) and by altering the palladium source (Table 1.1, entries 10 and 11), it was found that palladium(II) acetate and tricyclohexylphosphine were the best catalyst and ligand combination. The tetrafluoroborate salt of tricyclohexylphosphine was used as the precursor for this ligand. Furthermore, different bases were tested (Table 1.1, entries 12-17), including a stoichiometric amount of a pivalate salt to replace the combination of a substoichiometric amount of pivalic acid with a stoichiometric base, but all cases were inferior to K_2CO_3.

Table 1.1: Optimization of the reaction protocol for direct C–H arylation of BODIPY **1.4** (R = 2,6-dichlorophen-1-yl).



1.4 **1.5** **1.6**

			Reaction conditions[a,b]					Yield (%)[c]		
Entry	Catalyst	Ligand	Additive	Base	Solvent	X	Time	**1.4**	**1.5**	**1.6**
1	$Pd(OAc)_2$	PPh_3	-	K_2CO_3	toluene	Br	24 h	75	3	0
2	$Pd(OAc)_2$	PPh_3	-	K_2CO_3	toluene	Br	4 d	73	4	1
3	$Pd(OAc)_2$	PPh_3	AcOH	K_2CO_3	toluene	Br	24 h	76	3	1
4	$Pd(OAc)_2$	PPh_3	AcOH	K_2CO_3	toluene	Br	5 d	76	3	1
5	$Pd(OAc)_2$	PPh_3	PivOH	K_2CO_3	toluene	Br	24 h	59	15	3
6	$Pd(OAc)_2$	PPh_3	PivOH	K_2CO_3	toluene	Br	4 d	54	17	4
7	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$[d]	PivOH	K_2CO_3	toluene	Br	24 h	94	0	0
8[e]	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	toluene	Br	24 h	32	45	23
9	$Pd(OAc)_2$	DavePhos	PivOH	K_2CO_3	toluene	Br	24 h	68	0	0
10	$Pd_2(dba)_3$	PCy_3[d]	PivOH	K_2CO_3	toluene	Br	24 h	22	37	21
11	$Pd(TFA)_2$	PCy_3[d]	PivOH	K_2CO_3	toluene	Br	24 h	92	5	0
12	$Pd(OAc)_2$	PCy_3[d]	PivOH	Cs_2CO_3	toluene	Br	24 h	32	19	14
13	$Pd(OAc)_2$	PCy_3[d]	PivOH	Na_2CO_3	toluene	Br	24 h	92	5	1
14	$Pd(OAc)_2$	PCy_3[d]	PivOH	KOAc	toluene	Br	24 h	77	17	4
15	$Pd(OAc)_2$	PCy_3[d]	-	CsOPiv	toluene	Br	24 h	69	23	6
16	$Pd(OAc)_2$	PCy_3[d]	PivOH	Et_3N	toluene	Br	24 h	89	5	3
17	$Pd(OAc)_2$	PCy_3[d]	PivOH	Ag_2CO_3	toluene	Br	24 h	89	0	0
18	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	*o*-xylene	Br	24 h	28	45	22
19[f]	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	*o*-xylene	Br	24 h	22	41	26
20[g]	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	dioxane	Br	24 h	56	30	9
21	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	DMF	Br	3.5 h	20	0	0
22	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	DMF	Br	24 h	0	0	0
23	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	toluene	Cl[h]	4 d	94	2	0
24	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	toluene	I[h]	4 d	90	4	0
25	$Pd(OAc)_2$	PCy_3[d]	PivOH	K_2CO_3	toluene	OTf[h]	4 d	88	1	0

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophen-1-yl)-BODIPY **1.4**, 5 mol% catalyst, 10 mol% ligand, 30 mol% additive, 3 equivalents base, 1.1 equivalents pentadeuterated phenyl halide, 1 mL solvent, stirring for the indicated time at 110 °C. [b] R is 2,6-dichlorophen-1-yl. [c] All yields were estimated *via* NMR spectroscopy using pentadeuterated phenyl halides to avoid overlapping peaks. [d] HBF_4 salt of the phosphine ligand was used. [e] Highest yielding conditions. [f] Reaction was stirred at 144 °C. [g] Reflux in 1,4-dioxane, 101 °C. [h] No deuterated phenyl halide was used.

Varying the solvent (Table 1.1, entries 18-22) showed that apolar solvents like toluene and *o*-xylene gave the best results. Using *o*-xylene at 110 °C provided similar results as reflux in toluene (Table 1.1, entry 18), while reflux in *o*-xylene resulted in a slightly lower yield due to increased decomposition (Table 1.1, entry 19). It is possible to execute this reaction under microwave irradiation at 110 °C producing the monophenyl-BODIPY **1.5** in a significantly shorter time but in a somewhat lower yield than with conventional heating. Of the different aryl halides, bromoarenes were the best reagents. Reaction with chlorobenzene (Table 1.1, entry 23), iodobenzene (Table 1.1, entry 24) and phenyl triflate (Table 1.1, entry 25) only formed a trace amount of the desired product **1.5**.

Even under these optimized conditions, the yield of the monophenyl product **1.5** remains moderate. This can be rationalized by considering the reactivity of the C–H bonds on the 3,5-positions of BODIPY. Both positions are in fact identical to each other. Hence, so is the reactivity of the C–H bonds on these positions. Furthermore, this reactivity is not noticeably influenced by the introduction of a phenyl group during the reaction. Thus the C–H bond at the 3-position will be almost equally reactive in both the starting compound **1.4** and the 3-phenyl product **1.5**. As the reaction progresses the amount of starting material **1.4** will decrease, while that of the monophenylated dye **1.5** will increase. After about 24 hours the concentration of both compounds in the reaction mixture was observed to be equal. Due to their similar reactivity in C–H activation both compounds will react at a similar rate. Meaning the production rate of the 3-phenyl-BODIPY **1.5** will be equal to its consumption rate. Hence, after this point the concentration of the desired product remains constant, while the concentration of starting compound **1.4** keeps decreasing and that of the diphenyl sideproduct **1.6** keeps increasing. In other words, while reacting longer than 24 hours changes the composition of the reaction mixture, it does not result in more monophenyl product **1.5** and the maximum yield that can be obtained for this product is about 45%. After approximately 60 hours the reaction no longer noticeably progresses as all bromobenzene has been completely consumed.

3. Scope of the reaction

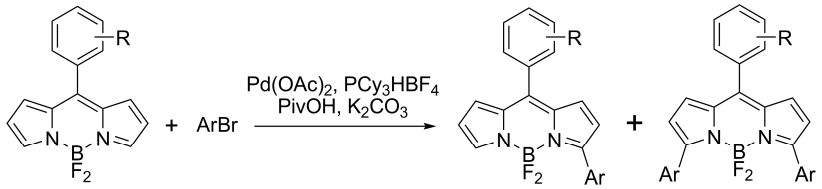
Using the optimized reaction conditions, the C–H arylation was tried with different bromoarene reagents (Table 1.2). Purification of the reaction was often cumbersome and time consuming because it contained a mixture of the starting compound **1.7**, the desired monoaryl dye **1.9** and the diaryl sideproduct **1.10** in similar amounts. With some reactions the separation of these compounds was incomplete as these dyes possessed very similar retardation factors. This further reduced the obtained yield due to mixed column chromatography fractions. Nonetheless, the monoaryl dye **1.9** could be obtained in a moderate yield for a range of bromoarenes.

Electron rich (Table 1.2, entries 2 and 5), heteroaromatic (Table 1.2, entries 5 and 11), sterically hindered (Table 1.2, entry 6) and ring-fused bromoarenes (Table 1.2, entry 7) are reactive in this C–H arylation reaction. In the case of 4-bromo-*N*,*N*-dimethylaniline **1.8d** (Table 1.2, entry 4) the desired product **1.9d** was formed, however this compound was unstable under the harsh reaction conditions and decomposed during the reaction. 4-Bromophenol **1.8c** on the other hand gave no reaction (Table 1.2, entry 3). This is presumably caused by deprotonation of the acidic phenol under the basic reaction condition, as 4-bromoanisole **1.8b** did react in a moderate yield (Table 1.2, entry 2). The other electron rich bromoarenes reacted in a similar yield as bromobenzene **1.8a** (Table 1.2, entry 1). The exception was the sterically hindered 2-bromo-1,3,5-trimethylbenzene **1.8f** (Table 1.2, entry 6), as it did not produce a diarylated product **1.10f** and only monoarylation, albeit in a lower yield, occured. This lower yield is probably caused by its higher steric hindrance making attack on the 3,5-positions of BODIPY more difficult, as can be observed from the longer reaction time needed to complete this reaction.

Disappointingly, reaction of very electron poor bromoarenes (Table 1.2, entries 8 and 9) proceeded extremely slowly. Although TLC analysis showed product formation for 4-bromobenzonitrile **1.8h** and 1-bromo-3-nitrobenzene **1.8i**, after 2 days there was not enough product formed to allow a complete characterization of the new compound. Hence, the majority of the starting material was recovered. Bromoarenes with less strongly electron withdrawing substituents on the other hand (Table 1.2, entries 10 and 11) could still react with BODIPY but the obtained yields

were lower than for electron rich bromoarenes. Although the yield of 1,4-dibromobenzene **1.8j** (Table 1.2, entry 10) was limited by oligomerization it introduced a bromo group onto the resulting dye **1.9j** that could potentially be used to further functionalize this compound.

Table 1.2: Scope of direct palladium catalyzed C–H arylation of BODIPY fluorophores **1.7** using bromoarenes **1.8**.[a]



Entry	Compound	R	Ar	Reaction time (h)	Yield (%)[b] **1.9**	**1.10**
1	**a**	2,6-Cl_2	phenyl[c]	24	44	17
2	**b**	2,6-Cl_2	4-anisyl	43	42	10
3	**c**	2,6-Cl_2	4-hydroxyphenyl	44	-[d]	-[d]
4	**d**	2,6-Cl_2	4-(dimethylamino)-phenyl	48	-[e]	-[e]
5	**e**	2,6-Cl_2	3-thienyl	27	55	10
6	**f**	2,6-Cl_2	mesityl	43	35	-[f]
7	**g**	2,6-Cl_2	1-naphthyl[c]	24	20[g]	16
8	**h**	2,6-Cl_2	4-cyanophenyl	48	trace	trace
9	**i**	2,6-Cl_2	3-nitrophenyl	48	trace	trace
10	**j**	2,6-Cl_2	4-bromophenyl	22	15	3
11	**k**	2,6-Cl_2	pyridin-4-yl	120	32	trace
12	**l**	H	phenyl[c]	28	31[g]	32
13	**m**	4-NO_2	phenyl[c]	46	28	18
14	**n**	2,4,6-Me_3	phenyl	48	22[g]	10[g]

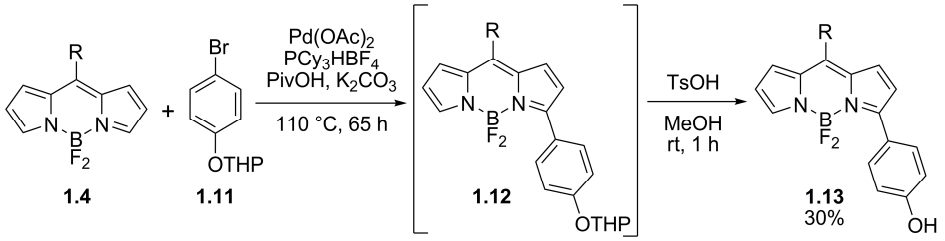
[a] Experimental conditions: 0.1 mmol BODIPY **1.7**, 5 mol% $Pd(OAc)_2$, 10 mol% PCy_3HBF_4, 30 mol% PivOH, 3 equivalents K_2CO_3, 1.1 equivalents bromoarene, stirring for the indicated time in 1 mL toluene at 110 °C. [b] All yields are isolated yields. [c] *o*-xylene is used as solvent at 110 °C. [d] No reaction occurred. [e] Product decomposed and could not be isolated. [f] No diarylated product was formed. [g] Low yield because of difficult purification.

To demonstrate the generality of the developed C–H arylation protocol, the reaction was also performed between different *meso*-substituted BODIPYs **1.7** and bromobenzene **1.8a**. This showed that not only the *meso*-2,6-dichlorophenyl derivative **1.7a** (Table 1.2, entry 1), but also the *meso*-phenyl **1.7l** (Table 1.2, entry 12), *meso*-(*p*-nitrophenyl) **1.7m** (Table 1.2, entry 13) and *meso*-mesityl **1.7n** (Table

1.2, entry 14) derivatives were reactive in this type of arylation. However, the products were formed in a slightly lower yield than for *meso*-2,6-dichlorophenyl-BODIPY **1.7a**.

All the previous reactions used a BODIPY dye that was substituted on its *meso*-position. These reactions showed that C–H activation occurred exclusively at the 3,5-positions of the dye and not at the other free 1,2,6,7-positions. In order to investigate if the *meso*-position is reactive in this transformation, a 1,3,5,7-tetramethyl-BODIPY was subjected to the developed palladium catalyzed C–H arylation with bromobenzene **1.8a**. Although the 8-position is unsubstituted in this molecule, no reaction was observed and the starting material was recovered. Hence, this position is not reactive under the used reaction conditions.

As mentioned above, 4-bromophenol **1.8c** is not reactive in the developed C–H arylation. Nevertheless, 3-(4-hydroxyphenyl)-BODIPY **1.13** can still be made if the acid phenol group is protected as a tetrahydropyranyl ether. Reaction of an 3,5-unsubstituted dye **1.4** with the protected bromoarene **1.11** forms the corresponding protected product **1.12**. Unfortunately, this product is unstable on silica gel and cannot be purified using column chromatography. Hence, the crude reaction mixture was deprotected with *p*-toluenesulfonic acid before purification, affording 3-(4-hydroxyphenyl)-BODIPY **1.13** in 30% yield (Scheme 1.3).



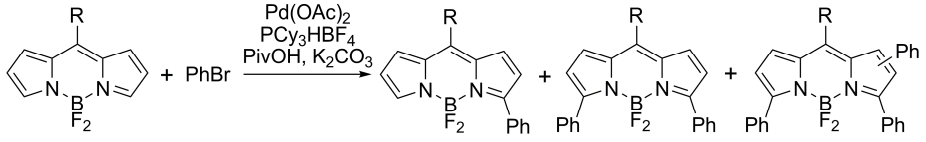
Scheme 1.3: Synthesis of 3-(4-hydroxyphenyl)-BODIPY using a protection/deprotection strategy (R = 2,6-dichlorophen-1-yl).

4. Extension to multiple arylations

As mentioned earlier, the current reaction protocol results in the formation of a mixture of three compounds. This limits the obtained yield of 3-monophenyl-BODIPY **1.5**. In order to synthesize an arylated dye in a better yield, it was tested whether the reaction could be pushed to diarylation using at least two equivalents of

bromobenzene over a longer reaction time to produce selectively 3,5-diphenyl-BODIPY **1.6**. Thus using the optimized reaction conditions for monoarylation with 2.5 equivalents of bromobenzene resulted in an acceptable yield of the desired diaryl product **1.6** after four days (Table 1.3, entry 2). Unfortunately, monophenyl-BODIPY **1.5** was still present in a significant amount, complicating purification and limiting the yield of the diphenyl dye **1.6**. Using a greater excess of bromobenzene did not improve the diarylation yield (Table 1.3, entry 3).

Table 1.3: Optimization of the reaction protocol for direct C–H diarylation of BODIPY **1.4** (R = 2,6-dichlorophen-1-yl).[a]



Entry	Equivalents					T	Time	Yield[b]			
	$Pd(OAc)_2$ (mol%)	PCy_3[c] (mol%)	PivOH (eq)	K_2CO_3 (eq)	PhBr (eq)	(°C)	(h)	**1.4** (%)	**1.5** (%)	**1.6** (%)	**1.14** (%)
1	5.0	10	0.30	3.0	2.5	110	24	13	41	36	0
2	5.0	10	0.30	3.0	2.5	110	96	3	32	53	0
3	5.0	10	0.30	3.0	5.0	110	95	6	33	49	0
4	12.5	25	0.75	7.5	2.5	144[d]	3	3	26	51	14
5	12.5	25	0.75	7.5	2.5	144[d]	24	0	2	44	44
6	12.5	25	0.75	7.5	2.5	110	24	3	29	56	7
7	12.5	25	0.75	7.5	2.5	110	96	0	8	55	29
8	10.0	20	0.60	6.0	2.0	110	24	5	34	50	3
9	10.0	20	0.60	6.0	2.0	110	96	0	17	48	27

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophen-1-yl)-BODIPY **1.4**, $Pd(OAc)_2$, $HPCy_3BF_4$, PivOH, K_2CO_3, pentadeuterated bromobenzene, reflux for the indicated time in 1 mL toluene. [b] All yields were estimated *via* NMR spectroscopy using pentadeuterated bromobenzene to avoid overlapping peaks. [c] HBF_4 salt of tricyclohexylphosphine was used. [d] Reflux in *o*-xylene.

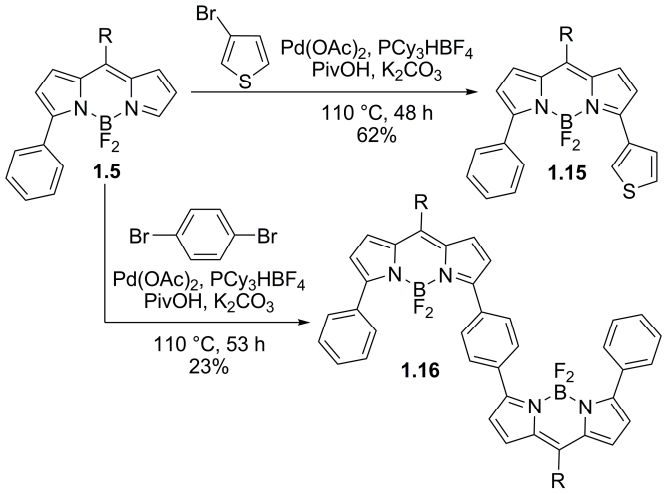
After four days the catalyst system was probably completely deactivated, hence the reaction stopped before 100% conversion was reached. In an attempt to push the reaction further, the amount of catalyst, ligand, pivalic acid and base were increased 2.5 times, by the same amount as the increase in equivalents of bromobenzene. Furthermore, to shorten the reaction time the reaction was done at a higher temperature in refluxing *o*-xylene. Using these forcing reaction conditions, all

starting material **1.4** was consumed after 24 hours and only a trace of monophenyl-BODIPY **1.5** remained. Unfortunately, not only the desired diphenyl dye **1.6** was present in the resulting reaction mixture, as also a triphenylated compound **1.14** was formed in a similar amount (Table 1.3, entry 5). The retardation factors of the diphenyl **1.6** and triphenyl fluorophores **1.14** are nearly identical making separation of these compounds implausible. Despite several attempts no pure sample of either dye could be obtained. The same forcing reaction after three hours gave a higher ratio of the desired diphenyl-BODIPY **1.6** (Table 1.3, entry 4), but purification of this dye remained unsuccessful. Attempts to push the reaction to triarylation by using even more bromobenzene, catalyst, *etc.* at an even higher temperature in refluxing 1,2-dichlorobenzene still provided a mixture of diphenyl **1.6** and triphenyl **1.14** compounds. The exact regiochemistry of the triphenyl product **1.14** could not be determined because no pure sample of this compound was available.

In order to still be able to isolate pure 3,5-diphenyl-BODIPY **1.6**, less forcing conditions were examined to hopefully avoid triarylation. Thus, reactions at a lower temperature of 110 °C (Table 1.3, entries 6-9) and without an excess of bromoarene (Table 1.3, entries 8 and 9) were tested. Regrettably, in all these experiments the triphenyl compound **1.14** remained present in varying degrees. Hence, the best procedure to synthesize and isolate 3,5-diphenyl-BODIPY **1.6** is the original attempt using the mono C–H arylation protocol with an excess of bromobenzene for four days (Table 1.3, entry 2). In this way, the diphenyl dye **1.6** could be isolated in a yield of 43%. This reaction can be significantly accelerated by using microwave irradiation at 110 °C instead of conventional heating, affording the desired product in a similar yield after 3.5 hours.

Lastly, the optimal arylation procedure was used to illustrate the possibilities of this novel palladium catalyzed C–H arylation reaction. To this end, an asymmetric dye **1.15** and a BODIPY dimer **1.16** were prepared using the developed protocol. The asymmetric system **1.15** was prepared by performing two successive C–H arylations, the first with bromobenzene **1.8a** (Table 1.2, entry 1), the second with 3-bromothiophene **1.8e** (Scheme 1.4). The second arylation proceeded in a much higher yield (62%) than the previous reactions, as overarylation was not an issue with the 3-substituted dye **1.5** under these conditions. Because this phenyl-substituted dye **1.5**

reacted with such a good yield, it was chosen as the substrate for a double C–H arylation with 1,4-dibromobenzene **1.8j**. Furthermore, the 3-substituent should prevent oligomerization side reactions. Hence, the reaction between the 3-phenyl dye **1.5** and 1,4-dibromobenzene **1.8j** resulted in the BODIPY dimer **1.16** in 23% yield (Scheme 1.4). Both the unsymmetrical dye **1.15** and this dimer **1.16** are structures that would be difficult to prepare using traditional strategies, such as from substituted pyrrole building blocks. Hence, their synthesis highlights the potential of our newly developed direct palladium catalyzed C–H arylation of BODIPY dyes.



Scheme 1.4: Synthesis of an asymmetric BODIPY and a BODIPY dimer using the developed palladium catalyzed C–H arylation (R = 2,6-dichlorophen-1-yl).

5. UV-vis spectroscopic properties

All the synthesized boron dipyrrin derivatives **1.9**, **1.10** and **1.15** are strongly colored solids that form intensely colored solutions with usually bright fluorescence upon irradiation. The variety of (het)aromatic groups at the 3,5,8-positions of the BODIPY core results in a set of fluorophores with absorption and fluorescence emission spectra covering a broad range of the visible spectrum, providing an opportunity to investigate the relationship between the structure and the spectroscopic properties of these dyes. The key results of this investigation are summarized here (Table 1.4 and Table 1.5).

For each dye, the spectra display the characteristic narrow absorption and fluorescence emission bands of classic boron dipyrromethenes. The shape of the emission band is the mirror image of the absorption band and both are separated by a small Stokes shift. In all cases, the fluorescence excitation spectra matched the absorption spectra. As a function of solvent, the spectral maxima are located within a very narrow wavelength range and are slightly red-shifted with increasing solvent polarizability. The visible absorption band is assigned to the $S_1 \leftarrow S_0$ transition. An additional, considerably weaker, broad absorption band can be observed in the UV spectral range and is attributed to the $S_2 \leftarrow S_0$ transition. Although the shapes of the spectra of all the studied BODIPYs are comparable, their absorption and emission maxima, Stokes shifts, absorption and emission bandwidths, and fluorescence quantum yields may be quite different, depending on the type of substituents on the 3,5,8-positions.

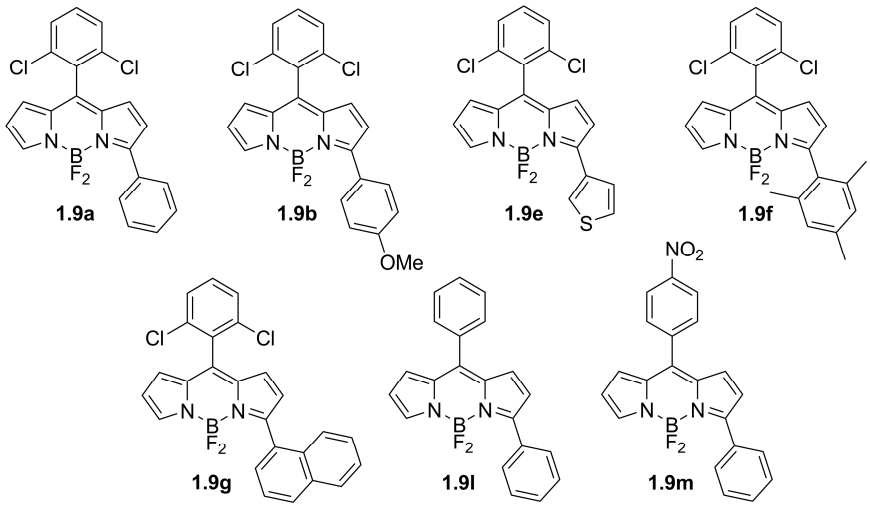


Figure 1.1: Structures of the 3-monoaryl-BODIPYs **1.9** for which the spectroscopic properties were measured.

Table 1.4: Spectroscopic data of 3-monoaryl-BODIPYs **1.9** in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f [e]
1.9a	MeOH	537	556	636	1281	1020	0.86
	MeCN	536	556	671	1305	1037	0.88
	EtOAc	539	558	632	1198	1003	0.89
	THF	542	561	625	1208	985	0.88
	Toluene	545	565	650	1237	1002	0.90
1.9b	MeOH	553	575	692	1587	1085	0.82
	MeCN	552	577	785	1631	1161	0.85
	EtOAc	555	577	687	1449	1053	0.86
	THF	558	579	650	1409	1061	0.86
	Toluene	562	583	641	1388	1015	0.88
1.9e	MeOH	551	565	450	1035	931	0.84
	MeCN	549	565	516	1074	941	0.88
	EtOAc	555	567	381	1017	944	0.87
	THF	555	570	474	994	930	0.86
	Toluene	559	575	498	979	930	0.97
1.9f	MeOH	516	531	547	861	1273	0.82
	MeCN	515	531	585	902	1287	0.85
	EtOAc	517	532	545	866	1287	0.85
	THF	518	534	578	872	1314	0.87
	Toluene	521	537	572	831	1304	0.89
1.9g	MeOH	524	574	1662	1810	1557	0.83
	MeCN	522	575	1766	1728	1752	0.85
	EtOAc	530	575	1477	1856	1498	0.85
	THF	537	579	1351	1906	1466	0.86
	Toluene	540	582	1336	1882	1364	0.90
1.9l	MeOH	524	547	802	1407	1344	0.02
	MeCN	523	547	839	1413	1292	0.02
	EtOAc	526	549	796	1377	1244	0.02
	THF	529	552	788	1367	1226	0.03
	Toluene	532	556	811	1346	1217	0.05
1.9m	MeOH	532	567	1160	1595	1905	0.01
	MeCN	531	571	1319	1587	1924	0.01
	EtOAc	534	571	1213	1548	1829	0.01
	THF	537	575	1231	1551	1821	0.01
	Toluene	541	578	1183	1528	1755	0.01

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* rhodamine 6G in methanol ($\Phi_r = 0.86$) as reference.

The nature of the *meso*-substituent has only a small effect on the positions of the spectral maxima. This is logical as the twisting of the *meso*-aryl substituent out of the BODIPY plane leads to poor conjugation between the aryl group and the boron dipyrrin core (General introduction, section 4). For the majority of the synthesized dyes, the fluorescence quantum yields are high ($\Phi_f > 0.85$), except for the analogues with *meso*-phenyl (in **1.9l** and **1.10l**) and *meso*-(*p*-nitrophenyl) (in **1.9m** and **1.10m**) substituents. Free rotation of the 8-aryl group in these dyes enhances nonradiative deactivation of the S_1 excited state, resulting in low fluorescence quantum yields (General introduction, section 4).[6] On the other hand, restriction of this rotation by steric hindrance between the chlorine atoms of a 8-(2,6-dichlorophenyl) group and the 1,7-hydrogens of the BODIPY core leads to high values for the fluorescence quantum yield. The presence of a nitro function on the *meso*-aryl group (in **1.9m** and **1.10m**) presents an extra contribution to fluorescence quenching.

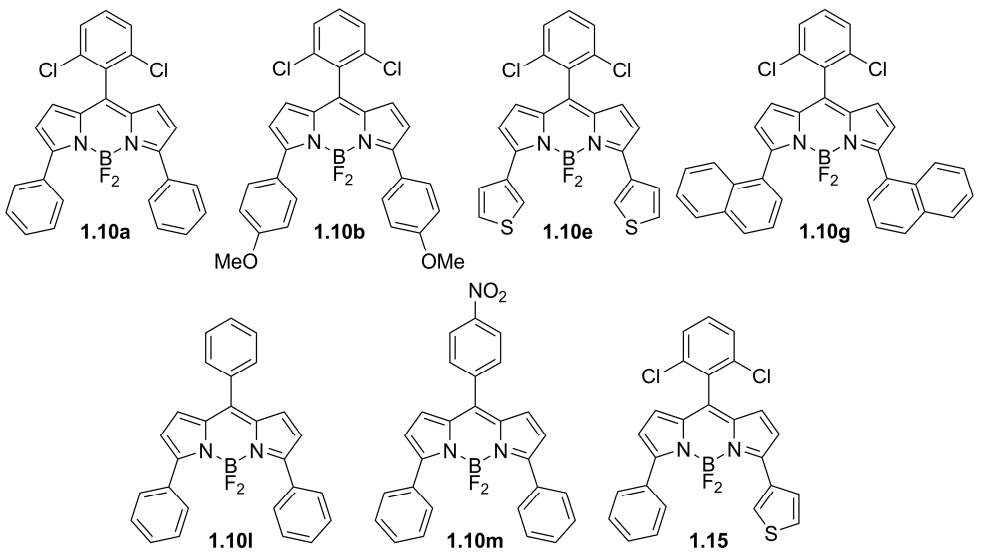


Figure 1.2: Structures of the 3,5-diaryl-BODIPYs **1.10** and **1.15** for which the spectroscopic properties were measured.

Table 1.5: Spectroscopic data of 3,5-diaryl-BODIPYs **1.10** and **1.15** in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f [e]
1.10a	MeOH	565	596	921	1494	977	0.85
	MeCN	561	597	1075	1544	1019	0.89
	EtOAc	566	598	945	1454	975	0.90
	THF	571	602	902	1431	942	0.89
	Toluene	573	605	923	1451	963	0.90
1.10b	MeOH	594	632	1012	1727	1000	0.86[f]
	MeCN	590	635	1201	1806	1090	0.93[f]
	EtOAc	596	633	981	1664	961	0.94[f]
	THF	600	637	968	1615	971	0.94[f]
	Toluene	603	637	885	1582	947	0.95[f]
1.10e	MeOH	597	619	595	1309	885	0.88[f]
	MeCN	597	620	621	1469	899	0.91[f]
	EtOAc	599	621	591	1291	872	0.94[f]
	THF	604	625	556	1224	851	0.94[f]
	Toluene	606	628	578	1228	832	0.98[f]
1.10g	MeOH	551	615	1889	2574	1538	[g]
	MeCN	542	615	2190	1925	1585	0.90
	EtOAc	554	616	1817	1987	1428	0.93
	THF	560	621	1754	2005	1368	0.87
	Toluene	565	623	1648	2022	1322	0.94
1.10l	MeOH	550	583	1029	1601	1070	0.17
	MeCN	546	583	1162	1631	1090	0.15
	EtOAc	551	585	1055	1540	1042	0.20
	THF	555	588	1011	1530	1030	0.20
	Toluene	558	591	1001	1502	1026	0.34
1.10m	MeOH	559	603	1305	1706	1455	0.02
	MeCN	556	601	1347	1740	1488	0.03
	EtOAc	560	603	1273	1677	1391	0.03
	THF	564	607	1256	1655	1397	0.03
	Toluene	569	610	1181	1632	1317	0.05
1.15	MeOH	580	609	821	1394	885	0.84
	MeCN	578	610	908	1509	896	0.89
	EtOAc	582	611	816	1360	871	0.90
	THF	587	615	776	1323	848	0.86
	Toluene	589	619	823	1314	842	0.91

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* rhodamine 6G in methanol (Φ_r = 0.86) as reference. [f] Φ_f determined *vs* cresyl violet in methanol (Φ_r = 0.55) as reference instead. [g] Not possible to obtain reliable Φ_f values due to very limited solubility in the indicated solvent.

In all cases, the 3-monoarylated **1.9** and 3,5-diarylated **1.10** BODIPY dyes have red-shifted absorption and emission spectra compared to their 3,5-unsubstituted precursors **1.7** (Figure 0.4, Table 1.4 and Table 1.5), with the diarylated compounds **1.10** showing the largest bathochromic shift. For example, the introduction of one phenyl group at the 3-position (in **1.9a**) produces a red-shift of approximately 29 nm in absorption and 35 nm in emission compared to unsubstituted compound **1.7a**. Incorporating a second phenyl group (in **1.10a**) entails an additional red shift of approximately 27 nm in absorption and 40 nm in emission. Hence, the introduction of two phenyl groups at the 3,5-positions leads to a total bathochromic shift of 56 nm in absorption and 75 nm in emission. These red-shifts reflect the increased length of the conjugation in the 3,5-diaryl dyes **1.10** relative to their 3-monoaryl counterparts **1.9** and evidently to the starting compound **1.7**. As mentioned earlier, substituting the 3,5-positions is the most effective way to increase the conjugation length in BODIPY dyes and thus introduce the largest bathochromic shifts (General introduction, section 4).

The various substituents on the 3,5-positions of the synthesized compounds lead to derivatives with absorption and emission spectra covering the visible region from green to red (Figure 1.3). Replacing the 3-phenyl substituent by electron donating *p*-anisyl (in **1.9b** and **1.10b**) or 3-thienyl (in **1.9e** and **1.10e**) groups results in an additional red-shift for both mono- and diarylation. On the other hand, the limited bathochromic shift caused by the 3-mesityl substituent (in **1.9f**) suggests that this mesityl group is twisted out of the BODIPY plane to minimize sterical interactions, thus severely restricting the conjugation between BODIPY and the mesityl group. Lastly, the absorption and emission maxima of 3-phenyl-5-thien-3-yl-BODIPY **1.15** are predictably the average of those of the 3,5-diphenyl **1.10a** and the 3,5-dithien-3-yl dyes **1.10e**.

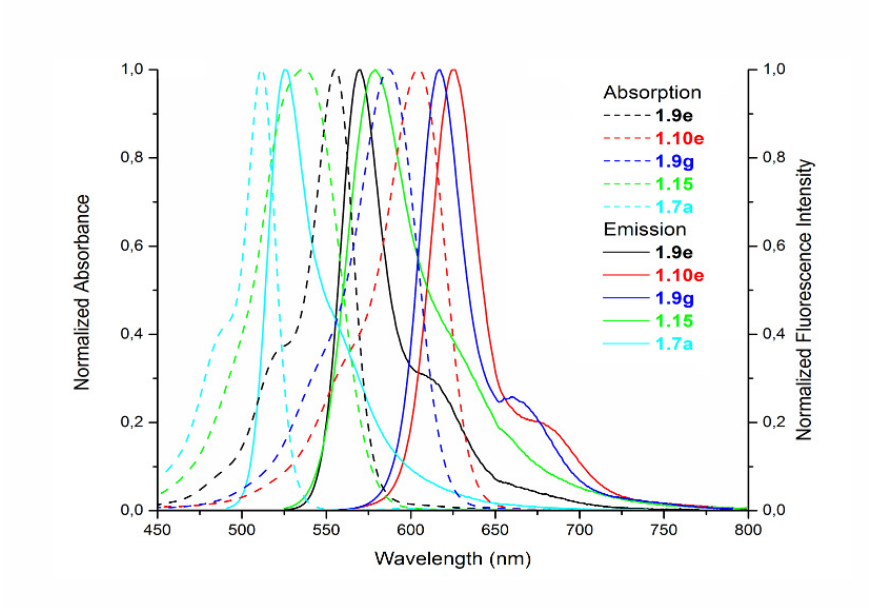


Figure 1.3: Normalized, visible absorption spectra and corresponding normalized fluorescence emission spectra of a selection of substituted *meso*-(2,6-dichlorophenyl)-BODIPY dyes (**1.7a**, **1.9e**, **1.10e**, **1.9g**, **1.15**) in THF.

6. Conclusion

A direct method for the preparation of brightly fluorescent red-shifted 3,5-arylated BODIPY dyes from 3,5-unsubstituted derivatives utilizing C–H functionalization has been developed. This method uses palladium(II) acetate and tricyclohexylphosphine as the catalyst and ligand together with a substoichiometric amount of pivalic acid in basic conditions in an apolar solvent at 110 °C. In this way, electron rich, heteroaromatic, sterically hindered and ring-fused bromoarenes can be selectively introduced onto the 3,5-positions of BODIPY without needing a tedious synthesis of substituted pyrrole building blocks or unstable intermediates.

Unfortunately, with most of these reactions a mixture of compounds was formed as diarylation was an important side reaction. This complicated the purification step and limited the obtained yield. Attempts to push the reaction to diarylation resulted in an inseparable mixture of diaryl and triaryl compounds. Nonetheless, by using an excess of bromoarene without pushing the reaction 3,5-diaryl-BODIPYs could be isolated in a moderate yield. Furthermore, this methodology was used in the synthesis of an

asymmetric system and a BODIPY dimer. Both compounds are structures that would be difficult to prepare using traditional strategies, highlighting the potential of our newly developed direct palladium catalyzed C–H arylation of BODIPY dyes.

7. References

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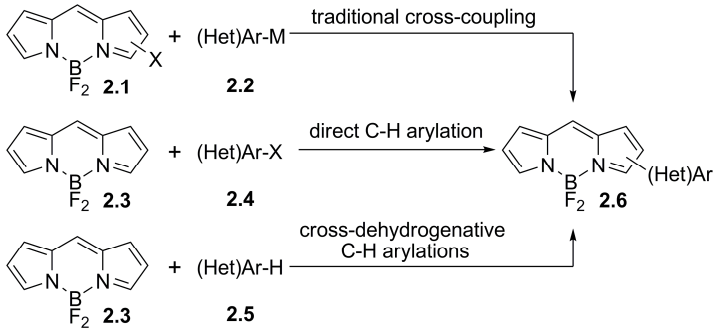
Chapter 2. Oxidative transformations of BODIPY dyes

1. Introduction

Transition metal catalyzed cross-coupling reactions have become very important methods to construct bi(hetero)aryl motifs **2.6**.[1] However, traditionally these reactions require preactivation of the two aromatic fragments, one as an aryl halide **2.1** and the other as an aryl organometal compound **2.2**. Incorporation of these activating functional groups can require several synthetic steps, generating waste and lowering the overall efficiency of the transformation. Therefore, direct arylation through cleavage of C–H bonds represent an environmental and economical attractive strategy, producing the desired bi(hetero)aryl compound **2.6** in a more efficient way.

With direct C–H arylation the organometal compound **2.2** is typically replaced by an unactivated arene **2.3**.[2] This arene reacts with an aryl halide **2.4** and is activated during the catalytic cycle in a C–H activation step. However, C–H functionalization can be taken even one step further, by replacing both the organometal compound **2.2** and the aryl halide **2.1** with an unactivated arene (**2.3** and **2.5)**. Both arenes are in this case activated during the reaction *via* C–H activation. Such transformations are called transition metal catalyzed cross-dehydrogenative C–H arylations and eliminate the need for any preactivation of the substrates.[3]



Scheme 2.1: Possible synthetic strategies towards (hetero)aryl substituted BODIPY dyes using traditional cross-coupling arylation, direct C–H arylation or cross-dehydrogenative C–H arylation reactions.

While direct C–H arylation of BODIPYs with bromoarenes has been developed (Chapter 1)[4] as well as a few other C–H functionalization reactions,[5] cross-

dehydrogenative C–H arylation of boron dipyrrins remains unexplored. To regenerate the catalyst and allow a catalytic cycle for cross-dehydrogenative reactions an external stoichiometric oxidant is required. However, not many oxidative transformations of boron dipyrromethenes are currently known, and thus not much is known about the stability of these dyes under oxidative conditions. The oxidative transformations currently reported for boron dipyrrins are oxidation of the 3,5-methyl groups,[6] oxidative nucleophilic substitution of hydrogen with monoalkyl and dialkyl amines as well as with enolates at the 3,5-positions[7] and palladium catalyzed C–H alkenylation at the 2,6-positions.[5a] Recently, a palladium catalyzed C–H arylation at the 2,6-positions was also described using benzoic acids in the presence of an oxidant.[5c]

Due to the encouraging results of our newly developed direct palladium catalyzed C–H arylation of BODIPY dyes (Chapter 1) as well as the unparalleled efficiency of cross-dehydrogenative C–H arylation, we set out to explore such oxidative transformations for boron dipyrrins. Furthermore, these experiments should provide insight into the stability of boron dipyrromethenes under oxidative conditions.

2. Cross-dehydrogenative C–H arylation

The challenge with cross-dehydrogenative arylation is that two C–H activation steps are needed to activate both coupling partners while both compounds contain multiple C–H bonds. To minimize regioselectivity issues it is important that these C–H bonds differ electronically from one another, so that in each compound only one C–H bond will preferentially react.[3] Our previously developed direct palladium catalyzed C–H arylation (Chapter 1)[4] illustrates that this is the case for BODIPY dyes, as only the 3,5-positions were reactive in the transformation. Such a good regioselectivity is common for heteroaromatic compounds as their C–H bonds are not electronically identical. Thus the coupling partner of BODIPY in cross-dehydrogenative C–H arylation should preferably also be a heteroaromatic compound. Furthermore, for a successful cross-dehydrogenative arylation dimerization of both the boron dipyrrin dye and the heteroaromatic compound should be avoided. This might be achievable if both coupling partners are significantly different form one another, with one being for example electron poor while the other is electron rich.[3] As boron dipyrromethenes are

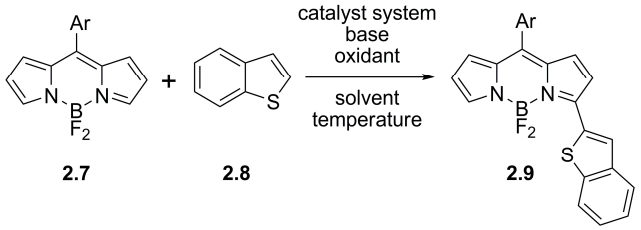
electron poor structures, the coupling partner should be an electron rich heteroaromatic compound.

For the initial experiment indole was chosen as the electron rich heteroaromatic coupling partner, as its benzene ring blocks one side of the pyrrole ring. This is important to prevent oligomerization, as this side reaction would complicate the obtained reaction mixture. The optimized conditions of our direct palladium catalyzed C–H arylation (Chapter 1)[4] were used for the test reaction, because these reaction conditions were proven to be compatible with boron dipyrromethenes. Lastly, copper(II) acetate was used as the stoichiometric oxidant. Reacting *meso*-2,6-dichlorophenyl BODIPY **2.7** with indole formed a trace amount of the desired product, however many side reactions occurred and pure product could not be isolated. Using 1-methylindole gave a similar result.

On the other hand, reacting the *meso*-2,6-dichlorophenyl dye **2.7** with 1-benzothiophene **2.8** resulted in a clean reaction, as no side reactions occurred. Thus benzo[*b*]thiophen-2-yl BODIPY **2.9** was isolated in a low yield of 8% after 24 hours (Table 2.1, entry 1), while the majority of the starting material was recovered. Reacting for a longer time did no significantly improve the resulting yield (Table 2.1, entry 2). Characterization of the formed product **2.9** showed that this reaction has the same regioselectivity as our direct palladium catalyzed C–H arylation, namely the reaction occurred exclusively at the 3-position of BODIPY.

As it was not certain if all reagents used in the trial reaction were needed for this transformation, several experiments were done in the absence of one of these compounds (Table 2.1, entries 3-6). Without either the catalyst or the ligand no reaction was observed, indicating that this is indeed a transition metal catalyzed reaction. When the base was left out arylation still occurred, but only a trace amount of product **2.9** was formed. On the other hand, reaction with or without pivalic acid resulted in the same amount of product being isolated, revealing that this compound plays no role in the catalytic cycle. Hence, further reactions were done without this additive.

Table 2.1: Optimization of the reaction protocol for cross-dehydrogenative C–H arylation of BODIPY **2.7** with 1-benzothiophene (Ar = 2,6-dichlorophen-1-yl).



Entry	Reaction conditions[a,b]							Yield
	Catalyst	Ligand	Additive	Base	Oxidant	Solvent	Time (h)	(%)[c]
1	$Pd(OAc)_2$	PCy_3[e]	PivOH	K_2CO_3	$Cu(OAc)_2$	toluene	24	8
2	$Pd(OAc)_2$	PCy_3[e]	PivOH	K_2CO_3	$Cu(OAc)_2$	toluene	70	10
3	-	PCy_3[e]	PivOH	K_2CO_3	$Cu(OAc)_2$	toluene	23.5	-[j]
4	$Pd(OAc)_2$	-	PivOH	K_2CO_3	$Cu(OAc)_2$	toluene	19.5	-[j]
5	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	$Cu(OAc)_2$	toluene	24	8
6	$Pd(OAc)_2$	PCy_3[e]	PivOH	-	$Cu(OAc)_2$	toluene	24	trace
7	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	CuO	toluene	23	trace
8[d]	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	toluene	21	16
9	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	Ag_2CO_3	toluene	23.5	trace
10	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	AgOAc	toluene	24	10
11	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	$K_2S_2O_8$	toluene	23	trace
12	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	Oxone®	toluene	23	trace
13	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	BQ[f]	toluene	21	-[j]
14	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	dioxane[g]	2	trace[k]
15	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	DMSO	1	-[l]
16	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	DMF	1	-[l]
17	$Pd(OAc)_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	diglyme	1.5	-[l]
18	$Pd(OAc)_2$	PCy_3[e]	-	Et_3N	Ag_2O	toluene	17	trace[m]
19	$Pd(TFA)_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	toluene	22	trace
20	$PdCl_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	toluene	22	trace
21	$(RhCp^*Cl_2)_2$	PCy_3[e]	-	K_2CO_3	Ag_2O	toluene	18.5	-[j]
22	$Pd(OAc)_2$	PPh_3	-	K_2CO_3	Ag_2O	toluene	18	trace
23	$Pd(OAc)_2$[h]	PCy_3[e,i]	-	K_2CO_3	-	toluene	21,5	trace
24	$Pd(OAc)_2$[h]	PCy_3[e,i]	-	K_2CO_3	Ag_2O	toluene	24	20

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophen-1-yl)-BODIPY **2.7**, 7 equivalents base, 7 equivalents oxidant, 5 equivalents 1-benzothiophene, 5 mol% catalyst, 10 mol% ligand, 30 mol% additive, 1 mL solvent, stirring for the indicated time at 110 °C. [b] Ar is 2,6-dichlorophen-1-yl. [c] All yields are isolated yields. [d] Highest yielding conditions. [e] HBF_4 salt of tricyclohexylphosphine was used. [f] 1,4-benzoquinone. [g] Reflux in 1,4-dioxane, 101 °C. [h] 1 equivalent of catalyst was used. [i] 1 equivalent of ligand was used. [j] No reaction occurred, starting material was recovered. [k] Mostly decomposition occurred, only a trace amount of product was isolated. [l] No arylation occurred, BODIPY was oxidized instead. [m] The majority of the starting material **2.7** formed an enamine-BODIPY **2.14** instead of the desired arylated dye.

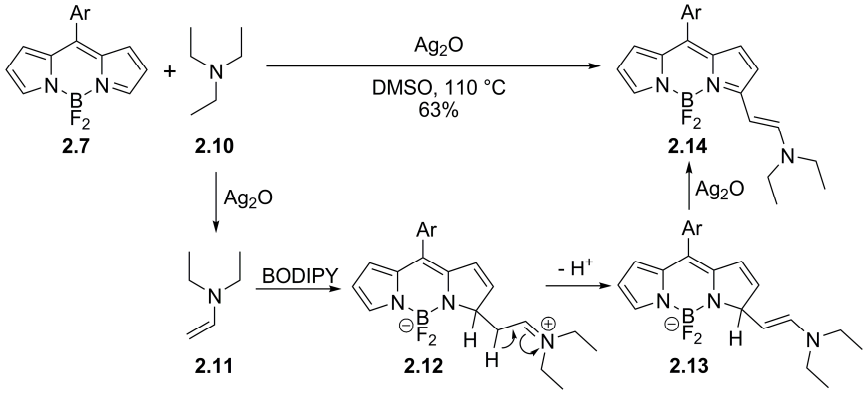
To improve the yield of this transformation other oxidants were tested (Table 2.1, entries 7-13). Most experiments resulted in only a trace amount of product **2.9**, whereas using silver acetate resulted in a similar yield as copper(II) acetate. The best oxidant was silver(I) oxide, providing the arylated product **2.9** in a slightly higher yield than for copper(II) acetate. When the reaction was done in 1,4-dioxane, instead of toluene, almost all starting material **2.7** decomposed and only a trace amount of product **2.9** was isolated (Table 2.1, entry 14). Using even more polar solvents, like DMSO, did not result in decomposition but it also did not provide any arylated dyes (Table 2.1, entries 15-17). In these cases, BODIPY itself was oxidized, instead of the catalyst, resulting in the formation of a 3-oxido dye **2.15** (see below, section 4). By replacing the potassium carbonate base with triethylamine, the yield of benzo[*b*]thiophenyl BODIPY **2.9** was also significantly reduced due to the occurrence of a side reaction (Table 2.1, entry 18). As a result of this side reaction in the presence of triethylamine, an enamine-BODIPY **2.14** was primarily formed under the used oxidative reaction conditions (see below, section 3). Lastly, a few other catalysts and ligands were tried (Table 2.1, entries 19-22), but for all examples either no reaction took place or only a trace amount of the desired product **2.9** was formed.

Even the best reaction conditions after the optimization, using silver(I) oxide, palladium(II) acetate, tricyclohexylphosphine and potassium carbonate in refluxing toluene, afforded the desired arylated compound **2.9** in only a low yield of 16% (Table 2.1, entry 8). Unfortunately, this value is too low to be synthetically useful. Electron rich heteroaromatic compounds can be introduced onto the BODIPY core in better yields using for example our developed direct palladium catalyzed C–H arylation (Chapter 1). To determine if this low yield is caused by an inefficient catalytic cycle, the reaction was redone using a stoichiometric amount of catalyst and ligand both with and without a stoichiometric oxidant (Table 2.1, entries 23 and 24). In the absence of oxidant only a trace amount of product **2.9** was isolated, suggesting that palladium(II) is not the active catalyst. On the other hand, in the presence of silver(I) oxide the arylated dye **2.9** was formed in a similar yield as when a catalytic amount of catalyst and ligand were used. This implies that the active species is in fact a palladium(IV) complex formed *in situ* by oxidation of palladium(II) acetate.[8] This

oxidation is probably inefficient due to the poor solubility of silver(I) oxide in toluene, hence the low yield for this transformation. However, when a more polar solvent is used BODIPY itself is oxidized instead. Thus it appears that the conditions needed to efficiently form the active catalytic species are incompatible with the stability of boron dipyrromethene dyes.

3. Oxidative nucleophilic substitution of hydrogen with triethylamine

As mentioned earlier, when cross-dehydrogenative C–H arylation was attempted in the presence of triethylamine **2.10** the arylation yield was significantly reduced due to the formation of a 3-enamine-BODIPY **2.14** (Table 2.1, entry 18). However, this product could not be isolated from the other products in the reaction mixture due to other side reactions that also took place. The formation of the enamine dye **2.14** can be rationalized by considering the mechanism of oxidative nucleophilc substitution of hydrogen (ONSH) on BODIPY (General introduction, section 3.2.2).[9] While triethylamine **2.10** itself is not reactive in an ONSH reaction with oxygen as the oxidant, it can be oxidized to the nucleophilic *N*,*N*-diethylethenamine **2.11** using a stronger oxidant.[10,11] This enamine **2.11** can react at the 3-position of BODIPY to form a σ^H-adduct **2.12**, that after deprotonation and oxidation becomes the enamine dye **2.14** (Scheme 2.2). A similar nucleophilic substitution reaction has recently been described between a *meso*-chloro BODIPY and triethylamine to form an 8-enamine dye.[11]



Scheme 2.2: Synthesis of a 3-enamine BODIPY using oxidative nucleophilic substitution of hydrogen with triethylamine (Ar = 2,6-dichlorophen-1-yl).

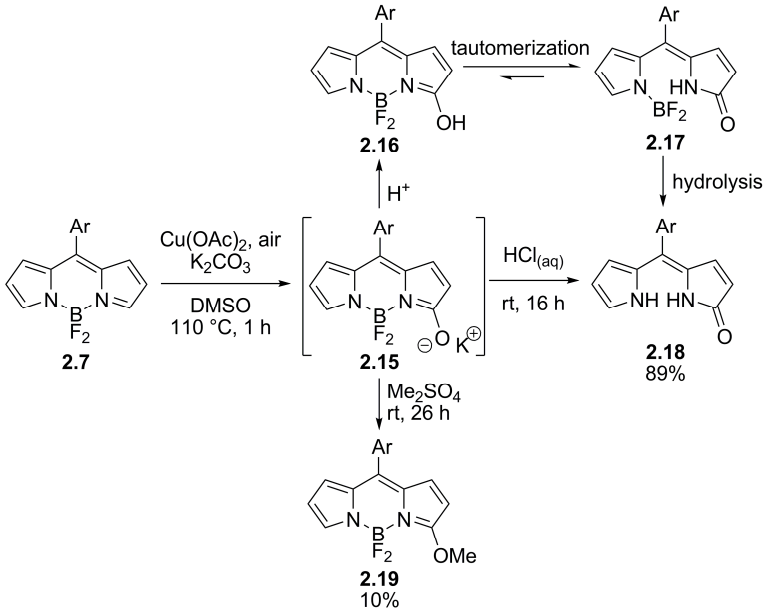
According to this proposed mechanism the palladium catalyst and phosphine ligand are not needed to allow this transformation. Indeed, reacting *meso*-2,6-dichlorophenyl BODIPY **2.7** with triethylamine **2.10** using only silver(I) oxide in DMSO at 110 °C afforded the enamine chromophore **2.14** in a good yield of 63% after 5 hours (Scheme 2.2). With the less oxidizing copper(II) acetate this yield was much lower (18%) and oxidation of BODIPY was observed to be a competing reaction (see below, section 4).

4. Oxidation of BODIPY in the synthesis of a new type of fluorophore

Another side reaction discovered during the optimization of the cross-dehydrogenative C–H arylation of BODIPY was the oxidation of the fluorophore **2.7** in polar solvents forming a 3-oxido dye **2.15** (Table 2.1, entries 15-17). A similar oxidation has been described for pyridines forming 2-pyridinones by heating pyridine in the presence of an oxidant, such as a copper(II) salt.[12] While the palladium catalyst and phosphine ligand were not needed for this transformation of BODIPY **2.7**, oxidant and base were required to form the oxidation product **2.15**. The purest reaction mixture was achieved in DMSO using copper(II) acetate as the oxidant and potassium carbonate as the base. However, also silver(I) oxide and manganese(III) acetate dihydrate were possible oxidants, while sodium hydroxide was a possible base. Triethylamine on the other hand, provided only a trace amount of the desired product **2.15**. Furthermore, it was discovered that this reaction was faster if done in the presence of air. In this case, the amount of copper oxidant could be reduced, although this metal salt remained necessary for the reaction to occur. Hence, copper(II) acetate could be used as a catalytic oxidant with oxygen as the stoichiometric reagent forming the oxidized product **2.15** in one hour (Scheme 2.3).

Unfortunately, the formed 3-oxido BODIPY **2.15** decomposed during the work up of the reaction. Nonetheless, when the reaction was done in deuterated dimethylsulfoxide, NMR analysis showed that the reaction mixture contained only one compound **2.15** once all starting material **2.7** was consumed. Hence, the *in situ* yield for this oxidation reaction is near quantitative. Moreover, in this DMSO solution the 3-oxido dye **2.15** was stable for over a month. Decomposition during work up is thus probably caused by protonation of the oxygen atom. The protonated

dye **2.16** can tautomerize to its enol form **2.17**, which is the boron difluoride complex of a dipyrrinone. The boron difluoride unit will only be weakly coordinated by the dipyrrinone ligand, as one of the nitrogens in this compound is protonated. Hence, the enol form **2.17** will be easily hydrolyzed to form a dipyrrinone **2.18** (Scheme 2.3).



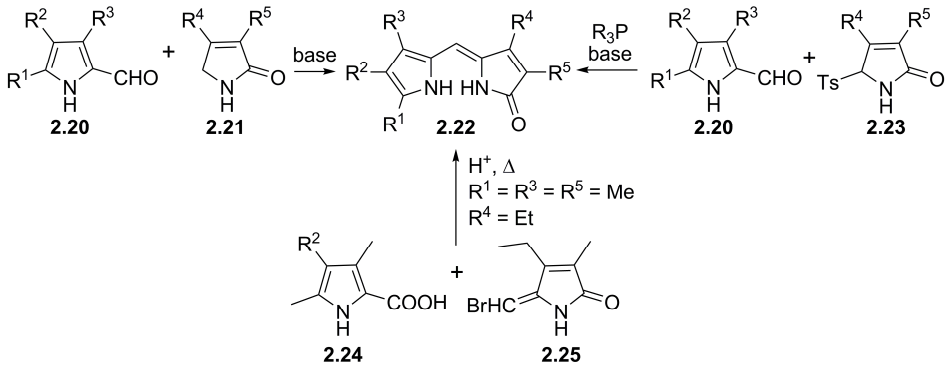
Scheme 2.3: Oxidation of BODIPY to a 3-oxido dye and subsequent decomposition to a dipyrrinone (Ar = 2,6-dichlorophen-1-yl).

Very recently, Yang *et al.* synthesized a similar 3-oxido-BODIPY by nucleophilic substitution of a 3,5-dichloro-BODIPY with sodium hydroxide and were able to isolate this dye as a stable sodium salt.[13] However, attempts to isolate our 3-oxido dye **2.15** as a salt were unfortunately unsuccessful, due to its good solubility in water. This is problematic as this oxido compound **2.15** in unstable in water and thus decomposes to the corresponding dipyrrinone **2.18**. However, it was possible to convert the 3-oxido-BODIPY **2.15** *in situ* to a methyl ether **2.19** by adding an excess of dimethyl sulfate after the oxidation and stirring 26 hours at room temperature (Scheme 2.3). Unfortunately, a lot of decomposition occurred during the methylation reaction and the 3-methoxy dye **2.19** was isolated in a low yield of 10%. Doing the methylation reaction at a higher temperature or using different methylating agents,

like methyl iodide or trimethyloxonium tetrafluoroborate, gave inferior results, forming either no product or a trace amount of product.

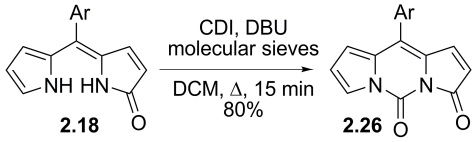
Other than methylation, it is also possible to form the main decomposition product of the 3-oxido-BODIPY dye **2.15**, the dipyrrinone **2.18**, *in situ* and to isolate this compound. This is done by adding aqueous hydrochloric acid to the reaction mixture once the oxidation is complete. In this way, the dipyrrinone **2.18** was isolated in an excellent yield of 89% after stirring the acidic reaction overnight at room temperature (Scheme 2.3). However, special care is needed during the purification of this compound, as a Z-E isomerization of the central double bond occurs under the influence of visible light.[14] Water appears to accelerate the decomposition of the oxidized dye **2.15**, as the same reaction in the absence of water using an excess of acetic acid requires heating at 110 °C for 42 hours to completely consume the 3-oxido fluorophore **2.15**. However, during the reaction with acetic acid a lot of side products were formed and no pure compound could be isolated.

This procedure presents a new methodology to make dipyrrinones. Currently, the most used and versatile method to synthesize these structures is a base catalyzed aldol condensation between a 2-formylpyrrole **2.20** and a 3-pyrrolin-2-one **2.21** (Scheme 2.4).[15,16] Both required starting materials can be made from pyrroles, *via* either a Vilsmeier reaction for the former or an oxidation for the latter.[17] Other possible strategies are either a Wittig-type reaction between a 2-formylpyrrole **2.20** bearing an electron withdrawing group and a 5-tosyl-3-pyrrolin-2-one **2.23** or an acid catalyzed condensation between a 3,5-dimethylpyrrole-2-carboxylic acid **2.24** and a bromomethylene pyrrolinone **2.25** (Scheme 2.4).[15] A few examples also use a lactam ring formation of an open chain substituent at 2-position of pyrrole or very rarely the oxidation of dipyrromethanes.[15] However, all of these strategies form dipyrrinones **2.22** that are unsubstituted at their central carbon (5-position). In contrast, our methodology produces a dipyrrinone **2.18** with an aryl group on this 5-position. Hence, this method provides access to a new type of dipyrrinones. Furthermore, using the rich functionalization chemistry of BODIPY (General introduction, section 3) it should be possible to make a broad range of functionalized dipyrrinones from the corresponding boron dipyrrin dyes.



Scheme 2.4: Literature procedures towards dipyrrinones.

Dipyrrinones are structural elements in bile pigments, and are thus often used in their synthesis or as models for these more complex molecules.[15] Furthermore, these compounds are also observed as a structural element in the products of porphyrinoids during their oxidative degradation.[15,18] Relatively recently, dipyrrinones have also been used as a starting material in the synthesis of a new type of fluorophores, called xanthoglows.[19] This was done by bridging the lactam and pyrrole nitrogens with a carbonyl function. This carbonyl bridge was introduced by reacting the dipyrrinone with 1,1'-carbonyldiimidazole (CDI) in the presence of a non-nucleophilic amine base, like DBU. 5-Aryldipyrrinone **2.18**, formed by oxidation of a BODIPY dye **2.7**, could be carbonylated using the same reaction conditions. In this way, a new fluorescent xanthoglow derivative bearing an aryl group was made in a good yield of 80% after 15 minutes (Scheme 2.5).



Scheme 2.5: Synthesis of a xanthoglow fluorophore by inserting a carbonyl bridge in a 5-aryldipyrrinone (Ar = 2,6-dichlorophen-1-yl).

5. Conclusion

A procedure allowing palladium catalyzed cross-dehydrogenative C–H arylation of BODIPY with benzothiophene was discovered. This method uses palladium(II) acetate and tricyclohexylphosphine as the catalyst and ligand together with an excess of silver(I) oxide and potassium carbonate in refluxing toluene. Unfortunately, the

yield for this transformation is low due to an inefficient oxidation of the catalyst in the used reaction conditions. On the other hand, in more polar solvents other reactions take place.

One of these reactions is an oxidative nucleophilic substitution of hydrogen with triethylamine and proceeds *via* an *in situ* formation of the enamine of triethylamine. By heating a *meso*-2,6-dichlorophenyl BODIPY at 110 °C in DMSO in the presence of a stoichiometric amount of triethylamine and silver(I) oxide the enamine chromophore could be isolated in a good yield.

The other reaction is an oxidation of BODIPY using a catalytic amount of copper(II) acetate in DMSO at 110 °C. Air oxygen was here the stoichiometric oxidant. The resulting 3-oxido-BODIPY could unfortunately not be isolated, as it decomposes to a dipyrrinone during the work up of the reaction. Nonetheless, the oxidation product could *in situ* be converted to this dipyrrinone using aqueous hydrochloric acid, and thus the dipyrrinone could be isolated in an excellent yield. Hence, this strategy provides a new way to make dipyrrinones, including the previously unavailable 5-aryldipyrrinone. Furthermore, this compound could be converted into a new type of fluorophore by inserting a carbonyl bridge between the two nitrogen atoms in a good yield.

6. References

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Chapter 3. C–H functionalization of BODIPY dyes using radical chain reactions

1. Introduction

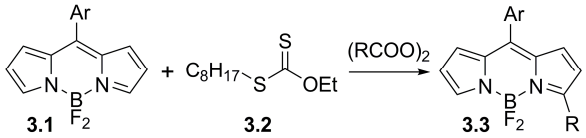
Transition metal catalyzed C–H functionalization of BODIPY dyes is an interesting strategy to make derivatives of this fluorophore and several of these transformations have been reported,[1] including our palladium catalyzed C–H arylation (Chapter 1).[2] Unfortunately, these methods have a few drawbacks, such as long reaction times, moderate yields and limited scopes. These shortcomings can be attributed to the rather forcing reaction conditions used in transition metal catalyzed C–H arylation in order to overcome the inertness of a C–H bond.

In contrast, radical C–H functionalization can occur under mild conditions, owing to the high reactivity of radicals.[3] Hence, radical reactions are important transformations to functionalize organic molecules.[4,5,6] However, radical functionalization of boron dipyrromethenes is virtually unknown. Only very recently, one isolated example, proposed to occur through an electrophilic radical species, has been reported to form a trifluoromethylated dye in a low yield.[7] Nonetheless, radical reactions on boron dipyrrin dyes could potentially be a superior alternative to transition metal catalyzed C–H functionalization, particularly due to the milder reaction conditions used in radical transformations. Hence, we set out to investigate the feasibility of functionalizing BODIPY fluorophores using radical chain reactions.

2. Reactivity of BODIPY towards radicals

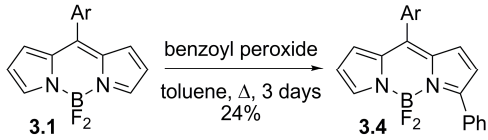
The majority of radical reactions of interest to synthetic chemists are chain processes in which radicals are generated by some initiation process, undergo a series of propagation steps generating new radicals and functionalizing a molecule at the same time.[3] One such reaction is based on the radical transfer of xanthates **3.2**, where the S-alkyl group is transferred from a xanthate to a different molecule.[5] Unfortunately, when *meso*-2,6-dichlorophenyl-BODIPY **3.1** was reacted with S-octyl xanthate **3.2**, using thermal decomposition of either dilauroyl peroxide or benzoyl peroxide as the initiation step, the desired octyl substituted dye did not form. Instead the radical of

the initiator attacked the boron dipyrromethene core directly rather than attacking the xanthate **3.2** (Scheme 3.1), forming a 3-undecyl-BODIPY in the case dilauroyl peroxide and a 3-phenyl-BODIPY **3.4** in the case of benzoyl peroxide. Similarly, initiating the radical reaction through oxidation of triethylborane with air at room temperature provided no desired octyl product. In this case, two products were observed as the ethyl radical of the initiator reacted at both the 3- and 5-positions, forming 3-ethyl- and 3,5-diethyl-BODIPY. In contrast with the other initiators, thermal decomposition of AIBN did not result in a new product and the starting material was recovered.



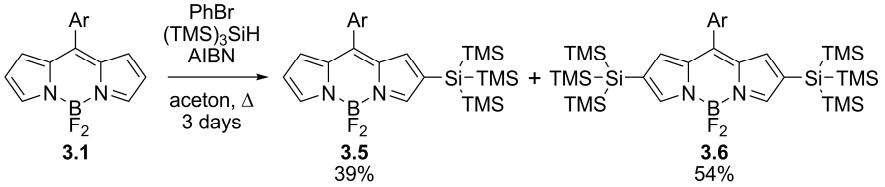
Scheme 3.1: Attempted alkylation of BODIPY *via* radical transfer of a xanthate (R = undecyl or phenyl, Ar = 2,6-dichlorophen-1-yl).

Although the above radical reactions provided new products **3.3**, isolating decent amount of these products as pure compounds was not possible. This was because only a catalytic amount of the initiator was used and because the purification was hindered by the occurrence of some side reactions. Nonetheless, the procedure could be modified to allow the synthesis and isolation of 3-phenyl-BODIPY **3.4** (Scheme 3.2). This was achieved by not adding a xanthate to the reaction mixture and by using an excess of benzoyl peroxide. However, the phenylation yield was lower than for our previously developed palladium catalyzed C–H arylation (Chapter 1).[2] Furthermore, it is more difficult to make derivatives of peroxides than of, for example, bromoarenes, making peroxides less useful as reagents. Therefore, optimization of this radical procedure was not pursued.



Scheme 3.2: Radical phenylation through thermal decomposition of benzoyl peroxide (Ar = 2,6-dichlorophen-1-yl).

Another type of radical chain reactions occurs through the reduction of an arylhalide with a tin hydride.[4] In fact, tributyltin hydride is the most commonly used reagent to conduct radical reactions. Unfortunately, *meso*-2,6-dichlorophenyl-BODIPY **3.1** decomposed completely in the presence of tributyltin hydride. The most common substitute for Bu_3SnH is tris(trimethylsilyl)silane, a non-toxic reagent that is commercially available and used in a growing number of radical reactions.[8] In contrast with tributyltin hydride, there was no decomposition of the boron dipyrrin dye **3.1** observed when this compound was used as the reductant. AIBN was chosen as the initiator of the radical reaction with bromobenzene because the previous experiments showed that the radicals of AIBN did not react with the BODIPY core. Unfortunately, the desired 3-phenyl dye **3.4** was not formed. Instead, the intermediate silyl radical of $(TMS)_3SiH$ reacted with the boron dipyrromethene core forming monosilylated **3.5** and disilylated dyes **3.6** in 39% and 54% respectively (Scheme 3.3).



Scheme 3.3: Attempted phenylation of BODIPY through the reduction of bromobenzene with tris(trimethylsilyl)silane (Ar = 2,6-dichlorophen-1-yl).

In the previous reactions the radicals of dilauroyl peroxide, benzoyl peroxide and triethylborane always reacted at the 3,5-positions of BODIPY, indicating that these positions are the most reactive towards radicals. However, with this reaction the silyl radical of $(TMS)_3SiH$ reacted instead at the 2,6-positions, as can be concluded from the crystal structure of the disilylated compound **3.6** (Figure 3.1). This is probably due to the size of the $(TMS)_3$silyl group, causing this bulky radical to attack the least sterically hindered 2,6-positions instead of the most reactive 3,5-positions.

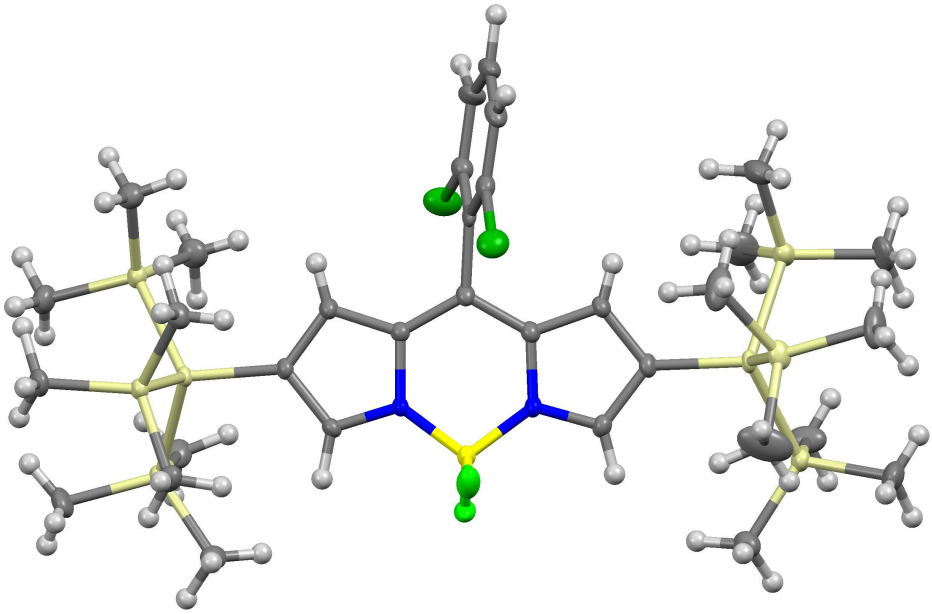
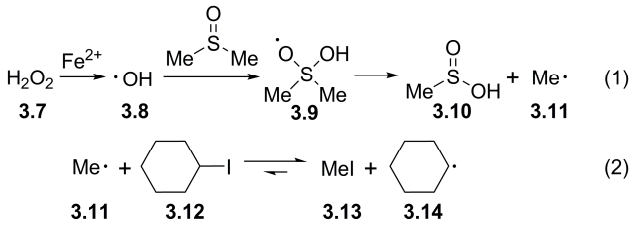


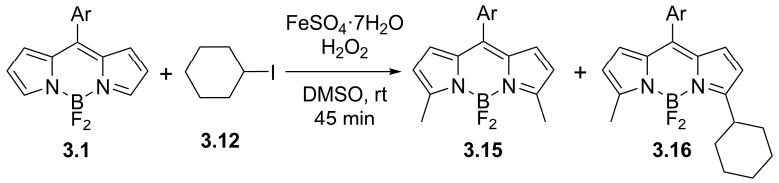
Figure 3.1: Molecular structure of 2,6-di(tris(trimethylsilyl)silyl)-BODIPY **3.6** as determined *via* X-ray diffraction.

In all the radical chain reactions described above, the desired radical never reacted with the BODIPY core. Instead the radical originating from the initiator or another intermediate radical attacked the chromophore before the desired radical could be formed. The only example where the desired radical actually substituted the dye was alkylation of BODIPY with iodocyclohexane **3.12** (Scheme 3.5). This reaction requires hydrogen peroxide **3.7** as the radical source together with a catalytic amount of iron(II) sulfate and uses DMSO as solvent and reagent.[6] Under these conditions a complex chain reaction occurs where the initial OH radical **3.8** is formed by the iron(II) catalyzed decomposition of hydrogen peroxide **3.7**.[9] This radical adds to the sulfoxide group of the solvent forming a radical adduct **3.9** which undergoes a fast β-scission forming a sulfinic acid **3.10** and a methyl radical **3.11** (Scheme 3.4, reaction 1).[10] The methyl radical reacts with iodocyclohexane **3.12** in an iodine exchange reaction forming the more stable cyclohexyl radical **3.14** that can subsequently attack an aromatic compound (Scheme 3.4, reaction 2).[11]



Scheme 3.4: Formation of a cyclohexyl radical from the reaction between iodocyclohexane, hydrogen peroxide, iron(II) sulfate and DMSO.

Carrying out this reaction with *meso*-2,6-dichlorophenyl-BODIPY **3.1** indeed led to a cyclohexyl substituted compound. Unfortunately, the cyclohexyl radical **3.14** was not the only radical that reacted with the dye. Also the intermediate methyl radical **3.11** substituted the fluorophore **3.1**. Hence, two major products were observed in the reaction mixture together with several minor products, preventing the isolation of a pure compound. Nonetheless, these two major compounds could be identified as 3,5-dimethyl-BODIPY **3.15** and 3-cyclohexyl-5-methyl-BODIPY **3.16** (Scheme 3.5). Thus also here the 3,5-positions of the dye were attacked by the formed radicals.



Scheme 3.5: Attempted cyclohexylation of BODIPY using iodocyclohexane, hydrogen peroxide, iron(II) sulfate and DMSO (Ar = 2,6-dichlorophen-1-yl).

3. Radical C–H methylation of BODIPY

The previous reaction gave a complex mixture of compounds because both cyclohexylation and methylation occurred simultaneously. By redoing the same reaction without iodocyclohexane **3.12**, cyclohexylation can be prevented so that only methylation takes place. In this way, a mixture of methylated dyes was formed. The major product in this mixture was the desired 3,5-dimethyl-BODIPY **3.15** (Table 3.1, entry 1).

The amount of dimethylated dye could be increased by reducing the catalytic loading (Table 3.1, entries 1-3), however without any iron(II) sulfate no reaction took place even after 3 hours (Table 3.1, entry 4). The methylation reaction could be

further improved by reducing the excess of hydrogen peroxide (Table 3.1, entries 5 and 6). In this way, the amount of 3,5-dimethyl-BODIPY **3.15** in the reaction mixture was increased to 85% (Table 3.1, entry 6). Unfortunately, for all of these conditions a small amount of monomethyl and trimethyl dyes was also present in this reaction mixture. The retardation factors of the monomethyl, dimethyl and trimethyl derivatives are very similar. Hence, despite multiple attempts, no pure sample of the dimethylated fluorophore **3.15** could be obtained.

Table 3.1: Optimization of the reaction protocol for radical dimethylation of BODIPY **3.1** (Ar = 2,6-dichlorophen-1-yl).[a]

3.1 **3.15**

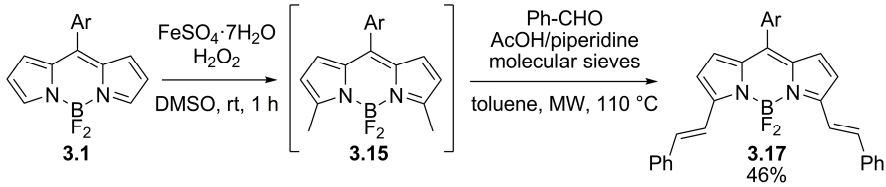
Entry	Equivalents		Time (min)	Yield (%)[b]
	$FeSO_4 \cdot 7H_2O$	H_2O_2		
1	10 mol%	3 eq	30	39
2	1 mol%[c]	3 eq	45	54
3	0.1 mol%[d]	3 eq	70	64
4	-	3 eq	200	-[e]
5	0.1 mol%[d]	2 eq	140	73
6[f]	0.1 mol%[d]	2.2 eq	70	85

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophen-1-yl)-BODIPY **3.1**, H_2O_2, $FeSO_4 \cdot 7H_2O$, stirred at room temperature for the indicated time in 1 mL DMSO. [b] All yields were estimated *via* NMR spectroscopy after initial purification of the crude mixture using column chromatography. [c] 0.1 mL of a 0.01 M $FeSO_4 \cdot 7H_2O$ solution in DMSO was added to the reaction mixture. [d] 0.1 mL of a 0.001 M $FeSO_4 \cdot 7H_2O$ solution in DMSO was added to the reaction mixture. [e] No reaction occurred. [f] Highest yielding conditions.

By using only 1.1 equivalents of hydrogen peroxide it was possible to make a reaction mixture that contained for 63% the 3-monomethyl-BODIPY together with the dimethyl derivative and the starting compound. But also here, separation of this mixture into pure compounds was not successful. Attempts to push the reaction to trimethylation using an excess of 6 equivalents of hydrogen peroxide resulted in an inseparable mixture of di- and trimethyl products after 3 hours. More highly

methylated dyes were not obsereved. After reacting 3 days all BODIPY dyes had decomposed.

The 3,5-methyl groups of BODIPY dyes are reactive in Knoevenagel type condensations with aromatic aldehydes forming styryl dyes (General introduction, section 3.2.2). Thus the unpurified reaction mixture of the dimethylation of boron dipyrromethene **3.1** can be used in such a reaction with an excess of benzaldehyde to form a mixture of styrylated dyes. The resulting styryl-BODIPYs have significantly different retardation factors from one another. Hence purification of the reaction mixture is now possible and the desired 3,5-distyryl-BODIPY **3.17** was isolated in a yield of 46% (Scheme 3.6). In this way, the radical methylation procedure can be used for the synthesis of 3,5-distyryl dyes from a 3,5-unsubstituted starting compound **3.1**. A direct styrylation of BODIPY dyes has been reported a few years ago using a vicarious nucleophilic substitution of hydrogen in a tandem reaction (General introduction, section 3.2.2).[12] However, that reaction allowed only monosubstitution from an unsubstituted dye and a nitrostyrene. In contrast, the procedure describe here provides access to the disubstituted derivatives starting from the same unsubstituted fluorophore **3.1** and an aromatic aldehyde.



Scheme 3.6: Synthesis of a 3,5-distyryl-BODIPY using radical methylation as an intermediate step.

4. Conclusion

Several radical chain reactions were tested to investigate the feasibility of functionalizing BODIPY fluorophores using such reactions. Although, in most cases, a reaction occurred, it was the radical formed from the initiator or another intermediate radical that attacked the chromophore before the desired radical could be formed. Thus it appears that boron dipyrromethenes are very reactive towards radicals. In fact these dyes are too reactive to successfully use a radical chain reaction. Hence, for radical reactions to succeed on this substrate and to be synthetically useful the desired radical should probably be formed in one step without

relying on a chain process. This might be achieved by using a one-electron redox reaction to convert a radical precursor directly into the desired radical.[4c,13]

Nonetheless, the high reactivity towards radicals can be used to connect BODIPY directly to a variety of initiators, forming for example a 3-phenyl dye, a 2,6-di(tris(trimethylsilyl)silyl) dye and a 3,5-dimethyl dye. However, the usefulness of these reactions is limited due to the limited set of available initiator systems. On the other hand, the reaction mixture containing 3,5-dimethyl-BODIPY could be further subjected to a Knoevenagel type condensation providing access to a 3,5-distyrylated dye from the 3,5-unsubstituted starting material. This makes the radical methylation of BODIPY in DMSO in the presence of hydrogen peroxide and a catalytic amount of iron(II) sulfate an interesting alternative strategy towards styrylated fluorophores.

5. References

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Chapter 4. Radical C–H arylation of BODIPY dyes using aryldiazonium salts

Part of this chapter is based on:

B. Verbelen, S. Boodts, J. Hofkens, N. Boens, W. Dehaen, *Angew. Chem., Int. Ed.* **2015**, *54*, 4612–4616.

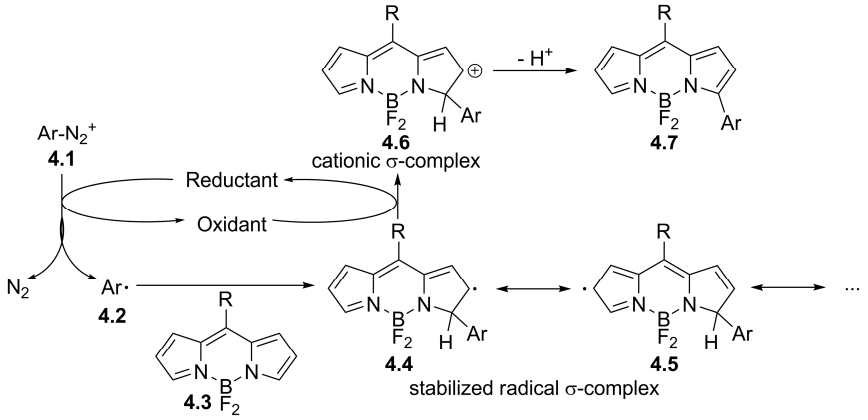
1. Introduction

Arylation at the 3,5-positions is an excellent way to create BODIPY dyes with a bathochromically shifted spectrum (General introduction, section 4). Unfortunately, traditional methods to synthesize such arylated dyes tend to suffer from the use of unstable intermediates and/or the need for a long synthetic route (General introduction, section 3). In contrast, we recently developed a palladium catalyzed C–H arylation at the 3,5-positions of BODIPY (Chapter 1),[1] providing brightly fluorescent 3,5-arylated boron dipyrrins in a single reaction step from simple building blocks. However, this method has a few drawbacks due to the rather forcing reaction conditions needed to overcome the inertness of a C–H bond during the C–H activation step. These drawbacks are a long reaction time, moderate yields and a scope limited to electron-rich bromoarenes.

Radical C–H arylation on the other hand can occur under mild conditions, owing to the high reactivity of aryl radicals **4.2**.[2,3] However, until now, radical arylation of boron dipyrrins has not been described. As concluded in the previous chapter, in order to have a successful radical substitution of the BODIPY core the aryl radical **4.2** should be formed without relying on a radical chain process (Chapter 3). This is possible by using an aryldiazonium salt **4.1** as a radical precursor. In fact, aryldiazonium salts are one of the well-known sources of aryl radicals through a homolytic dediazoniation mechanism, mostly achieved by means of a reduction (Scheme 4.1).[4,5] Hence, the use of aryldiazonium salts for the arylation of BODIPY dyes could prove to be an interesting strategy to synthesize new derivatives of this fluorophore. Therefore, we set out to investigate the feasibility of radical C–H arylation on readily available *meso*-substituted BODIPY dyes **4.3** using aryldiazonium salts **4.1**.

2. Optimization of the reaction

The most frequently used method to generate aryl radicals **4.2** from aryldiazonium salts **4.1** is through reduction with a copper(I) salt.[4] Accordingly, this approach was selected as the starting point for our study of the radical C–H arylation of the BODIPY core. Since boron dipyrrins are mostly insoluble in water, acetone was chosen as the initial solvent. Reaction of 8-(2,6-dichlorophenyl)-BODIPY **4.8a** with excess benzenediazonium tetrafluoroborate **4.9** and one equivalent of copper(I) chloride at room temperature resulted after 25 hours in the desired diphenylated compound **4.10a** in a low yield of 13% (Table 4.1, entry 2).



Scheme 4.1: Proposed mechanism for radical arylation of BODIPY dyes using aryldiazonium salts and the stabilization of the intermediate BODIPY radical.

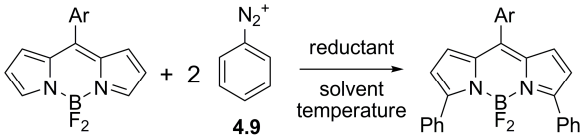
Characterization of the formed product revealed that the phenyl radicals reacted exclusively at the 3,5-positions of the boron dipyrromethene core. The same regioselectivity has been observed for other radical reaction with BODIPY dyes (Chapter 3). This selectivity can be compared with the exclusive 2-addition of radical species to electron deficient alkenes. Only the radical intermediate formed by addition to the 2-position of the alkene is stabilized by the electron withdrawing group. In the case of a boron dipyrrin, addition to the 3-position of one pyrrole group will form a radical that is stabilized by delocalization over several double bonds and by the electron withdrawing imine part, aided by the complexed boron difluoride group, of the adjacent pyrroline (as shown in resonance form **4.5**, Scheme 4.1). Moreover, such a high selectivity in radical reactions is also known for protonated

heteroaromatic bases.[3] This is accounted for by the strong increase in polarity of these heteroaromatic bases when protonated, causing polar effects to determine the outcome of the reaction. A similar reason can be used to explain the observed selectivity in the radical C–H arylation of the BODIPY core, because the BF_2-group can be seen as a strongly polarizing Lewis acid complexed with a dipyrromethene base.

The limited yield of the trial reaction might be caused by the used reductant, because copper(I) chloride can react with diazonium salts in a Sandmeyer reaction.[6] In order to improve the yield, and because the use of a reducing agent is needed (Table 4.1, entry 1), other copper(I) sources were tried (Table 4.1, entries 3 and 4). This showed that the presence of a halide in the copper(I) salt greatly reduced the obtained yield. Furthermore, it became apparent that the use of a more soluble copper(I) salt markedly shortened the required reaction time. Copper(0) and a copper(II) salt were also tested as respectively a reductant or a precursor thereof (Table 4.1, entries 5 and 6). However, $CuCl_2$ proved incapable of initiating the radical reaction and copper(0) resulted in a lower yield than for a non halide copper(I) salt.

Besides copper(I), other reducing agents have the required reduction potential to be able to reduce a diazonium salt.[4] The most common of these reductants were tested (Table 4.1, entries 5-10), and the most notable of these experiments was the use of ferrocene ($FeCp_2$), because it gave an immediate reaction. Unfortunately, the yield in this case was only moderate due to a significant amount of arylation of the formed ferricinium cation, resulting in the formation of phenylferrocene and diphenylferrocene.[7] Hence, to limit this competing reaction, the experiment was redone with less ferrocene. This initially led indeed to an improved yield (Table 4.1, entry 11). However, further lowering to a catalytic amount of ferrocene gave incomplete dediazoniation, probably due to insufficient regeneration of the ferrocene catalyst (Table 4.1, entry 12). To counter the deactivation of the catalyst, we investigated continuous addition of ferrocene to maintain a constant low concentration of reducing agent (Table 4.1, entries 13-17). Of the different addition speeds tested, 0.2 mmol/h gave the best result (Table 4.1, entry 16) providing the diphenylated product **4.10a** in less than an hour in an excellent yield of 84%.

Table 4.1: Optimization of the reaction protocol for radical C–H arylation of BODIPY **4.8a** using a benzenediazonium salt **4.9** (Ar = 2,6-dichlorophen-1-yl).[a]



4.8a **4.9** **4.10a**

Entry	Reductant	Addition speed of reductant	Solvent	Total reaction time	Yield (%)[b]
1	-	-[c]	acetone	20 h	trace
2	CuCl (0.10 mmol)	-[c]	acetone	25 h	13
3	$Cu(PPh_3)_3Br$ (0.10 mmol)	-[c]	acetone	1.5 h	36
4	CuTC[d] (0.10 mmol)	-[c]	acetone	1.5 h	63
5	Cu(0) (0.25 mmol)	-[c]	acetone	2 h	32
6	$CuCl_2$ (0.10 mmol)	-[c]	acetone	18.5 h	trace
7	Hydroquinone (0.10 mmol)	-[c]	acetone	21.5 h	trace
8	L-Ascorbic acid (0.25 mmol)	-[c]	acetone	21 h	24
9	$FeSO_4$ (0.10 mmol)	-[c]	acetone	23.5 h	trace
10	$FeCp_2$ (0.10 mmol)	-[c]	acetone	20 min	41[e]
11	$FeCp_2$ (0.05 mmol)	-[c]	acetone	1 h	54
12	$FeCp_2$ (0.01 mmol)	-[c]	acetone	20 h	44
13	$FeCp_2$ (0.05 mmol)	0.025 mmol/h	acetone	2 h	49
14	$FeCp_2$ (0.05 mmol)	0.05 mmol/h	acetone	105 min	57
15	$FeCp_2$ (0.05 mmol)	0.1 mmol/h	acetone	75 min	74
16[f]	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	acetone	45 min	84
17	$FeCp_2$ (0.05 mmol)	0.6 mmol/h	acetone	30 min	72
18	$FeCp_2$ (0.10 mmol)	0.2 mmol/h	acetone	1 h	83
19	$FeCp_2$ (0.025 mmol)	0.2 mmol/h	acetone	75 min	48
20[g]	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	acetone	45 min	67
21	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	DMF	40 min	50
22	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	MeCN	2 h	32
23	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	EtOH	40 min	32
24	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	CH_2Cl_2	19.5 h	16
25	-	-	DMSO	20 min	71
26[h]	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	acetone	45 min	55
27[i]	$FeCp_2$ (0.05 mmol)	0.2 mmol/h	acetone	2.5 h	58

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophenyl)-BODIPY **4.8a**, 0.25 mmol benzenediazonium tetrafluoroborate **4.9**, reductant, 1 mL of solvent, stirring for the indicated time at room temperature. [b] All yields are isolated yields. [c] Reductant was added immediately. [d] Copper(I) thiophene-2-carboxylate. [e] The yield was only moderate due to the competing arylation of ferrocene, as observed *via* mass spectrometry (EI mode). [f] Highest yielding conditions. [g] 0.21 mmol of diazonium salt was used. [h] The reaction was done at 0 °C. [i] Benzenediazonium hexafluorophosphate was used instead of the tetrafluoroborate salt.

To complete the optimization, the total amount of added ferrocene (Table 4.1, entries 18 and 19), the amount of diazonium salt **4.9** (Table 4.1, entry 20), the solvent (Table 4.1, entries 21-25), and the temperature (Table 4.1, entry 26) were varied. Yet, none of these experiments afforded a further improvement. One notable experiment was the reaction in DMSO. In this case, as soon as BODIPY **4.8a** and the diazonium salt **4.9** were dissolved in this solvent the reaction changed color. The diazonium salt **4.9** was consumed within minutes, even though no ferrocene was added to the solution. Analysis of the reaction mixture showed that the desired diphenyl dye **4.10a** was formed. However, this was a messy reaction and a lot of other products were also present. Nonetheless, the 3,5-diphenyl-BODIPY **4.10a** could be isolated in a good yield of 71%. This result can be explained by considering the electron donating properties of DMSO.[8] In fact, this solvent can form a charge transfer complex with diazonium ions. The resulting complex can decompose *via* an electron transfer from DMSO to the diazonium ion forming an aryl radical that can substitute a substrate, as has been reported before.[9] Hence, in this case the solvent is the reductant and thus no ferrocene was needed for this reaction.

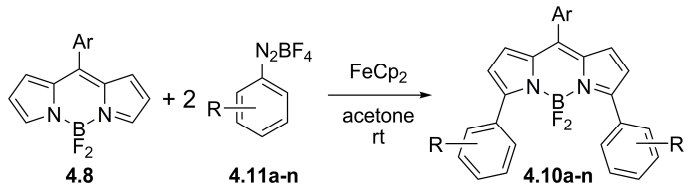
All these reactions have used benzenediazonium tetrafluoroborate as the source of the phenyl radical. However, the same reaction using benzenediazonium hexafluorophosphate also provides the desired diphenyl dye **4.10a** (Table 4.1, entry 27). However, the hexafluorophosphate salt does not completely dissolve under the used reaction conditions. Hence, it takes longer for the reaction to go to completion, allowing decomposition of the diazonium salt to compete with the arylation reaction. This slower reaction is probably the reason for the lower yield with a hexafluorophosphate anion compared with a tetrafluoroborate diazonium salt.

3. Scope of the reaction

Using the optimized reaction conditions, the radical C–H arylation was executed with different BODIPY substrates and a range of aryldiazonium tetrafluoroborates (Table 4.2), illustrating the broad scope of this reaction. Different *meso*-substituted boron dipyrromethenes were reactive in this type of arylation providing the phenylated product **4.10a-c** in good to excellent yields (Table 4.2, entries 1-3).

The three isomers of nitrobenzenediazonium tetrafluoroborate **4.11d-f** all yielded the desired compounds **4.10d-f**, with those diazonium salts with a directly conjugated 4-nitro and 2-nitro substituents resulting in higher yields than the one with a cross-conjugated 3-nitro group (Table 4.2, entries 4-6). Other electron-poor diazonium salts **4.11g-i** were also reactive using the optimized conditions up to a yield of 86% (Table 4.2, entries 7-9). Of particular interest are the bromo **4.10h** and carboxy products **4.10i**, because both functionalities allow further derivatization through transition metal catalyzed cross-coupling and esterification/amidation reactions, respectively. Moreover, 3,5-bis(4-carboxyphenyl)-BODIPY **4.10i** is a water soluble fluorophore in its deprotonated form. Hence, this radical arylation provides an easy access to water soluble dyes with red-shifted UV–vis absorption and emission spectra (see below).

Table 4.2: Scope of radical C–H diarylation of BODIPY dyes **4.8** using aryldiazonium salts **4.11**.



4.8 **4.11a-n** **4.10a-n**

Entry	Compound	Ar	R	Reaction time (min)	Yield (%)[b]
1	**a**	2,6-dichlorophen-1-yl	H	45	84
2	**b**	phenyl	H	45	60
3	**c**	mesityl	H	45	65
4	**d**	2,6-dichlorophen-1-yl	4-NO_2[c]	30	77
5	**e**	2,6-dichlorophen-1-yl	3-NO_2	60	51
6	**f**	2,6-dichlorophen-1-yl	2-NO_2[c]	40	72
7	**g**	2,6-dichlorophen-1-yl	4-CN	40	86
8	**h**	2,6-dichlorophen-1-yl	4-Br[c]	40	53
9	**i**	2,6-dichlorophen-1-yl	4-COOH	45	69
10	**j**	2,6-dichlorophen-1-yl	benzo[*c*]	45	54
11	**k**	2,6-dichlorophen-1-yl	2-Ph[d]	90	50
12	**l**	2,6-dichlorophen-1-yl	2,4,6-Me_3	150	19
13	**m**	2,6-dichlorophen-1-yl	4-OMe	50	30
14	**n**	2,6-dichlorophen-1-yl	4-NMe_2[e]	180	35[f]

[a] Experimental conditions: 0.1 mmol BODIPY **4.8**, 0.25 mmol diazonium salt **4.11**, 0.05 mmol $FeCp_2$ (0.2 mmol/h), 1 mL acetone, stirring for the indicated time at room temperature. [b] Isolated yield. [c] 0.2 mmol diazonium salt **4.11** and 0.04 mmol $FeCp_2$ were used. [d] Reaction was done on a 0.4 mmol scale. [e] $Fe(Cp^*)_2$ was used as reducing agent. [f] Isolated yield of monoarylated compound, diarylated compound is only formed in trace amount.

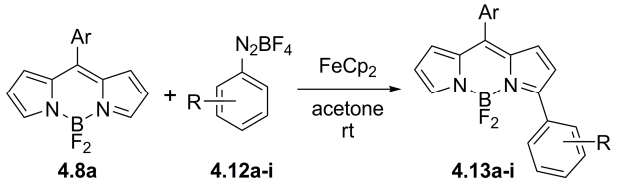
Not only electron-poor diazonium salts can be used in this transformation. Both the ring-fused naphthalene-2-diazonium tetrafluoroborate **4.11j** and the sterically hindered biphenyl-2-diazonium **4.11k** and 2,4,6-trimethylbenzenediazonium **4.11l** tetrafluoroborates resulted in the corresponding 3,5-diarylated compounds **4.10j-l** (Table 4.2, entries 10-12). However, the strong steric hindrance of the mesityl group made the last reaction less effective. A three times longer reaction time was needed to give the dimesityl product **4.10l** in a low yield of 19%. Furthermore, 4-methoxybenzenediazonium salt **4.11m** gave the diaryl product **4.10m** in a moderate yield (Table 4.2, entry 13). This lower yield was probably caused by a reduced reactivity of the more electron-rich monoarylated intermediate, hindering the second arylation step. 4-(Dimethylamino)benzenediazonium salt **4.11n** proved to be too electron-rich to be reduced by ferrocene. By using the more reducing decamethylferrocene, reaction did occur. However, after complete consumption of the diazonium salt only a trace amount of the diarylated compound **4.10n** was formed and the monoarylated product **4.13i** was isolated instead in a yield of 35% (Table 4.2, entry 14).

These results demonstrate the vast improvement of the present radical C–H arylation compared to our previous palladium catalyzed alternative (Chapter 1).[1] For example, this new method provides easy access to compounds that could not be made using the palladium catalyzed reaction, such as arylated products with electron-withdrawing functionalities **4.10d-i**, a dimesitylated dye **4.10l** and a derivative with a 4-(dimethylamino)phenyl substituent **4.10n**. Furthermore, this new procedure supplies the desired dyes in a much shorter reaction time and with a significantly higher yield. The present radical C–H arylation is also superior to other synthetic strategies toward 3,5-diaryl-BODIPYs, such as those starting from 2-arylpyrroles[10] and those using a Suzuki or Stille reaction with 3,5-dihalogenated BODIPYs.[11] Indeed, our radical C–H arylation forms the desired arylated compound **4.10** in one atom economical step, thus eliminating the need for a multi-step synthesis. Furthermore, high reaction temperatures, long reaction times and unstable pyrrole intermediates are avoided with this new procedure.

For these radical C–H arylation reactions a BODIPY dye that was substituted on its *meso*-position was always used. As mentioned before, the aryl radicals reacted

exclusively with the 3,5-positions of this *meso*-substituted dye **4.8** and not with the other free 1,2,6,7-positions. In order to investigate if the *meso*-position can react with aryl radicals, 1,3,5,7-tetramethyl-BODIPY was subjected to the radical arylation reaction with benzenediazonium tetrafluoroborate **4.11a**. Despite that the 8-position is unsubstituted in this molecule, no reaction was observed and the starting material was recovered. Hence, this position does not react with an aryl radical under the used reaction conditions.

Table 4.3: Scope of radical C–H monoarylation of BODIPY **4.8a** using aryldiazonium salts **4.12** (Ar = 2,6-dichlorophen-1-yl).[a]



4.8a **4.12a-i** **4.13a-i**

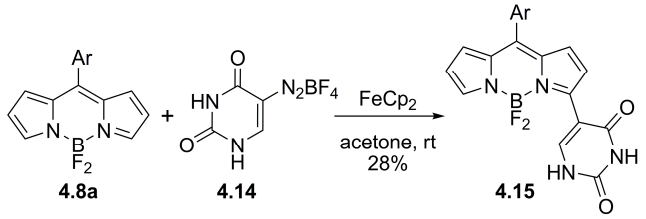
Entry	Compound	R	Reaction time (min)	Yield (%)[b]
1	**a**	H	35	58
2	**b**	4-NO_2	35	50
3	**c**	2-NO_2[c]	45	51
4	**d**	4-CN	40	74
5	**e**	4-COOH	35	53
6	**f**	benzo[*c*]	40	53
7	**g**	2,4,6-Me_3	105	52
8	**h**	4-OMe	40	41
9	**i**	4-NMe_2[d]	105	26

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophenyl)-BODIPY **4.8a**, 0.1 mmol diazonium salt **4.12**, 0.02 mmol $FeCp_2$ (0.2 mmol/h), 1 mL acetone, stirring for the indicated time at room temperature. [b] Isolated yield. [c] Reaction was done on a 0.4 mmol scale. [d] $Fe(Cp^*)_2$ was used as reducing agent.

The procedure developed for diarylation can be modified to allow radical C–H monoarylation (Table 4.3). This was achieved by using one equivalent of diazonium salt instead of an excess and reducing simultaneously the amount of ferrocene. In this way, the monoarylated product **4.13a**, formed by reaction between BODIPY **4.8a** and benzenediazonium tetrafluoroborate **4.12a**, could be isolated in 58% yield. Similarly, electron-poor diazonium salts reacted in good yields (Table 4.3, entries 2-5), *e.g.*, up

to 74% in the case of 4-cyanobenzenediazonium tetrafluoroborate **4.12d**. Ring-fused and sterically hindered diazonium salts also resulted in the formation of the desired products in comparable yields (Table 4.3, entries 6 and 7). In the case of electron-rich diazonium salts, the resulting yields were unfortunately somewhat lower (Table 4.3, entries 8 and 9). Due to the identical reactivity of the 3- and the 5-hydrogens some overarylation occurs in all these examples, producing the corresponding diarylated compound **4.10** as a side product in an estimated yield between 5 and 15%, depending on the used diazonium salt.

A broad range of diazonium salts can functionalize BODIPY using our procedure. Unfortunately, reaction with heteroaromatic diazonium salts, like quinoline-3-diazonium and 2-(methoxycarbonyl)thiophene-3-diazonium tetrafluoroborate, resulted in complex mixtures from which the desired product could not be isolated. Just like boron dipyrromethenes, heteroaromatic compounds are substrates for radicals.[3,12] Hence, arylation of the heteroaromatic ring will be a competing reaction. The combination of arylation of BODIPY and arylation of the heteroaromatic compound is what probably creates the complex reaction mixture. The only example where a pure product could be isolated was the reaction between *meso*-(2,6-dichlorophenyl)-BODIPY **4.8a** and uracil-5-diazonium tetrafluoroborate **4.14** (Scheme 4.2). A mixture of compounds was still formed with this reaction. However, arylation with a polar uracil group created a large enough difference in the retardation factors of the formed product to allow purification when 1 equivalent of the diazonium salt **4.14** was used, producing a 3-(uracil-5-yl)-BODIPY adduct **4.15** in 28% yield. When an excess of the uracil-5-diazonium salt **4.14** was used to push the reaction to diarylation, the reaction mixture became again very complex and isolation of a pure compound was no longer possible.

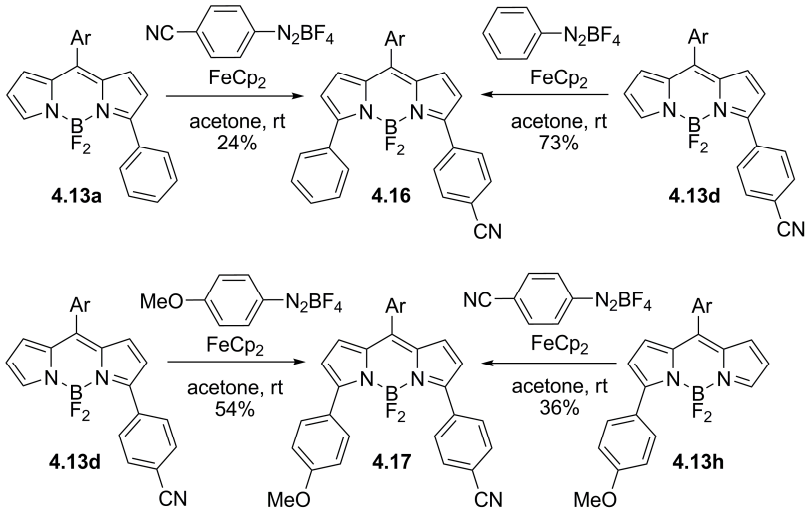


4.8a **4.14** **4.15**

Scheme 4.2: Synthesis of a 3-(uracil-5-yl)-BODIPY using radical C–H arylation (Ar = 2,6-dichlorophen-1-yl).

4. Applications

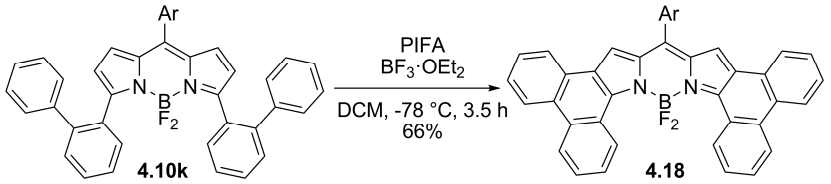
In order to illustrate the potential of the newly developed radical C–H arylation, two asymmetrically substituted dyes (**4.16** and **4.17**) were synthesized using this method (Scheme 4.3). 3-Phenyl-BODIPY **4.13a** was reacted with excess 4-cyanobenzenediazonium tetrafluoroborate **4.12d**. Unfortunately, the starting compound **4.13a** was insufficiently soluble in the reaction solvent, resulting in an incomplete reaction and hence a low yield. When the reaction order was reversed and 3-(4-cyanophenyl)-BODIPY **4.13d** was combined with benzenediazonium tetrafluoroborate **4.12a**, this problem was avoided. Thus, the desired 3-(4-cyanophenyl)-5-phenyl-BODIPY **4.16** was isolated in a good yield of 73%. 3-(4-Cyanophenyl)-BODIPY **4.13d** could also be used in the synthesis of 3-(4-cyanophenyl)-5-(4-methoxyphenyl)-BODIPY **4.17** *via* reaction with 4-methoxybenzenediazonium tetrafluoroborate **4.12h**. Separation of the desired product **4.17** of this reaction from a small amount of starting material **4.14d** proved to be very tedious. Thus 54% of the product was isolated as pure compound and the rest was lost as mixed column chromatography fractions. The same asymmetrical dye **4.17** was also prepared from 3-(4-methoxyphenyl)-BODIPY **4.13h**. However, in analogy with the synthesis of 3,5-di(4-methoxyphenyl)-BODIPY **4.10m**, compound **4.13** was not reactive enough to give a complete conversion resulting in a lower yield. Both synthesized asymmetrical fluorophores described here are compounds that are a challenge to prepare with previously reported methodologies (General introduction, section 3). Hence, the current radical C–H arylation allows the synthesis of sophisticated BODIPY dyes in a straightforward fashion.



Scheme 4.3: Synthesis of asymmetrical 3,5-diarylated BODIPY dyes using radical C–H arylation (Ar = 2,6-dichlorophen-1-yl).

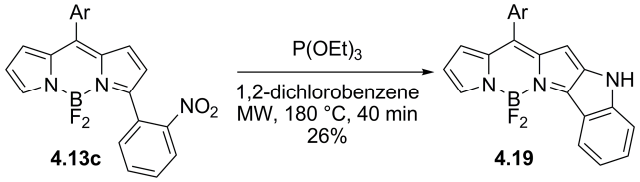
Radical C–H arylation can also be used in the synthesis of annulated dyes, by providing easy access to the required starting materials. Annulation, *i.e.* the building of a ring onto some molecule, is a strategy to extend the conjugation in a dye.[13,14,15] This conjugation is more effective than with a similar non fused aromatic substituent, because ring fusion forces the substituent into the same plane as the dye. Thus annulated dyes possess larger red-shifts than the corresponding arylated dyes. Furthermore, ring fusion reduces nonradiative decay caused by rotational relaxation and increases the molar absorption coefficient. Hence annulated chromophores are also very bright fluorophores.

Using the radical C–H arylation protocol, 3,5-bis(biphenyl-2-yl)-BODIPY **4.10k** can be made in a good yield from a 3,5-unsubstituted dye **4.8a** and biphenyl-2-diazonium tetrafluoroborate **4.11k** (Table 4.2, entry 11). The resulting diaryl fluorophore can be used to make an annulated dye **4.18** *via* an oxidative cyclization with phenyliodine bis(trifluoroacetate) (PIFA) at -78 °C.[14,16] This reaction proceeded smoothly and provided a bis(biphenyl)-fused BODIPY **4.18** in a good yield of 66% (Scheme 4.4). Hence, an annulated dye was synthesized form a simple boron dipyrromethene **4.8a** in only two reaction steps.



Scheme 4.4: Synthesis of a bis(biphenyl)-fused BODIPY dye (Ar = 2,6-dichlorophen-1-yl).

Another way to build a ring on a molecule involves a reductive cyclization of a nitro-compound in the presence of a suitable organophosphorus reagent. This method is commonly referred to as the Cadogan cyclization.[17,15] The required starting compounds bearing 2-nitrophenyl groups were synthesized radically from a 3,5-unsubstituted dye **4.8a** and 2-nitrobenzenediazonium tetrafluoroborate **4.11f** (Table 4.2, entry 6 and Table 4.3, entry 3). When 3,5-di(2-nitrophenyl)-BODIPY **4.10f** was refluxed in 1,2-dichlorobenzene in the presence of an excess of triethyl phosphite, reaction took place and the annulated product was slowly formed. Unfortunately, the formed product proved to be unstable under the reaction conditions. By the time the reaction was complete there was no product left. Luckily, the reaction could be significantly accelerated by doing the transformation instead under microwave irradiation at 180 °C. In this way, not all molecules of the annulated product had decomposed after complete conversion. The desired bisindole-fused dye was sadly too insoluble to be successfully purified from the formed side products. Nonetheless, reacting 3-(2-nitrophenyl)-BODIPY **4.13c** using the same reaction conditions allowed the synthesis of the monoindole-fused analog **4.19**. The solubility of this fluorophore was not as poor as the bisannulated dye and hence this product could be isolated in a yield of 26% (Scheme 4.5). This strategy is another example of a simple synthesis of an annulated chromophore after a radical C–H arylation step starting from a standard BODIPY dye **4.8a**.



Scheme 4.5: Synthesis of an indole-fused BODIPY dye (Ar = 2,6-dichlorophen-1-yl).

5. Aromatic amine as arylating reagent

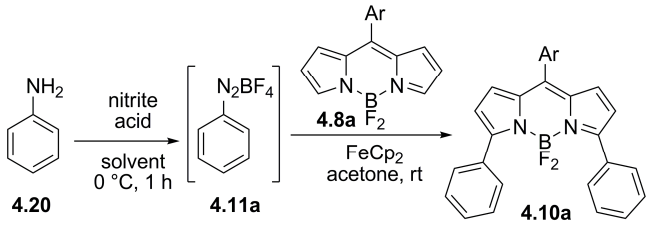
Most aryldiazonium salts are not commercially available. Hence they need to be prepared from the corresponding aromatic amines. Isolating aryldiazonium compounds requires extra care as the dry solids of the less stable diazonium salts are rather explosive. Furthermore, in order to store these compounds they need to be cooled and kept dry. Thus it is common practice not to isolate these salts at all and instead use the reaction mixture immediately for the next synthetic step.[18]

A similar strategy was examined for our radical C–H arylation. Benzenediazonium tetrafluoroborate **4.11a** was formed *in situ* from aniline **4.20** using different literature procedures (Table 4.4). After reacting one hour at 0 °C, the concentrated solution was diluted with acetone and BODIPY **4.8a** was added to the solution. Next, ferrocene was added dropwise according to the previously optimized conditions (section 2). Using a Brønsted acid to make the intermediate nitrosonium ion from either an inorganic nitrite in water (Table 4.4, entry 1) or an organic nitrite in ethanol (Table 4.4, entry 3) resulted in the formation of the desired diphenyl dye **4.10a** in the second step. However, under these acidic conditions a significant amount of deborylation occurred, forming the dipyrromethene of the diphenyl dye **4.10a**. Separating the desired BODIPY dye **4.10a** from the corresponding dipyrromethene is tedious and not always successful. This deborylation side reaction combined with a difficult purification limits the obtained yield for the examples using a Brønsted acid.

On the other hand, using Lewis acid boron trifluoride diethyl etherate to generate a nitrosium ion from an organic nitrite in dichloromethane[19] did not result in deborylation of the BODIPY product (Table 4.4, entry 4). Hence, the desired diphenyl dye **4.10a** was isolated in a better yield of 53%. In order to simplify the procedure, the diazotization with boron trifluoride was tried in the solvent of the second reaction step (Table 4.4, entries 5 and 6). After one hour, this reaction in acetone was brought to room temperature and BODIPY **4.8a** and ferrocene were added. Unfortunately, the diazotization in acetone with boron trifluoride diethyl etherate proved to be very slow. After BODIPY **4.8a** and ferrocene were added and the reaction was stirred for one hour, only a trace of the diphenyl dye **4.10a** was formed. However, reacting for a longer time resulted in a larger amount of product.

As the reduction of the intermediate diazonium salt with ferrocene is a fast reaction, this can only be due to a continued formation of the diazonium compound in the presence of boron dipyrrin and ferrocene.

Table 4.4: Optimization of the reaction protocol for radical C–H arylation of BODIPY **4.8a** using aniline **4.20** in a sequential one-pot procedure (Ar = 2,6-dichlorophen-1-yl).[a]



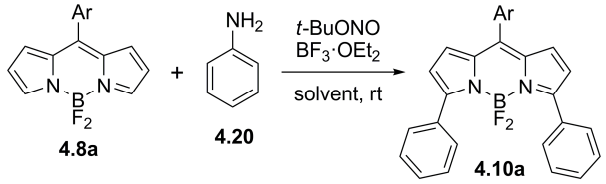
Entry	Nitrite source	Acid	Solvent	Time of step 2	Yield (%)[b]
1	$NaNO_2$ (2.5 eq)	HBF_4[c] (3.3 eq)	H_2O (0.05 mL)	45 min	37[d,e]
2	*i*-PentONO (4.1 eq)	HBF_4[c] (5.5 eq)	AcOH (0.25 mL)	35 min	trace[f]
3	*i*-PentONO (3.0 eq)	HBF_4[c] (7.5 eq)	EtOH (0.20 mL)	45 min	36[d]
4	*t*-BuONO (3.0 eq)	$BF_3{\cdot}OEt_2$ (3.8 eq)	DCM (0.20 mL)	50 min	53
5	*t*-BuONO (3.0 eq)	$BF_3{\cdot}OEt_2$ (3.8 eq)	acetone (2.5 mL)	1 h	trace
6	*t*-BuONO (3.0 eq)	$BF_3{\cdot}OEt_2$ (3.8 eq)	acetone (2.5 mL)	18 h	40

[a] Experimental conditions for step 1: 0.25 mmol (2.5 equivalents) aniline **4.20**, nitrite source, acid, solvent, stirring one hour at 0 °C. Experimental conditions for step 2: add acetone (total volume 1 mL), 0.1 mmol BODIPY **4.8a**, 0.05 mmol $FeCp_2$ (0.2 mmol/h), stirring for the indicated time at room temperature. [b] Isolated yield. [c] Used as a 50 % solution in water. [d] Dipyrromethene was formed as a side product. [e] Yield estimated using NMR spectroscopy. [f] BODIPY **4.8a** dissolves poorly in this AcOH/H_2O/acetone mixture.

This last result suggests that a nonsequential one-pot procedure, forming and reducing the intermediate diazonium salt **4.11a** in parallel, might be possible. This would be a simpler protocol to arylate BODIPYs using aromatic amines. When a 3,5-unsubstituted boron dipyrromethene **4.8a** and aniline **4.20** were stirred in acetone at room temperature in the presence of *tert*-butyl nitrite, boron trifluoride diethyl etherate and ferrocene the desired diphenyl compound **4.10a** was formed in a low yield (Table 4.5, entry 1). The low yield of this reaction was due to a competing arylation of ferrocene[7] which was, like the same reaction using an isolated aryldiazonium salt (section 2), an important side reaction. Because the intermediate diazonium salt **4.11a** is continuously formed at an unknown rate, it would be very difficult to limit the arylation of ferrocene by slow addition of this reductant. Hence

other reductants were tried to improve the yield for this one-pot procedure. The second best metal based reductant from the optimization of the original reaction (section 2) was copper(I) thiophene-2-carboxylate, unfortunately using this salt for a nonsequential one-pot arylation gave only a trace amount of product **4.10a** (Table 4.5, entry 2).

Table 4.5: Optimization of the reaction protocol for radical C–H arylation of BODIPY **4.8a** using aniline **4.20** in a nonsequential one-pot procedure (Ar = 2,6-dichlorophen-1-yl).[a]



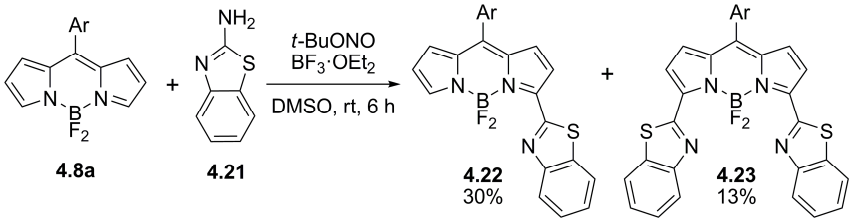
Entry	Amount of Aniline (eq)	Reductant	Solvent	Time (h)	Yield (%)[b]
1	3.0	$FeCp_2$ (0.5 eq)	acetone[c]	24.5	20
2	3.0	CuTC[d] (1.0 eq)	acetone[c]	22	trace
3	3.0	-	DMSO	6	64
4	2.5[e]	-	DMSO	5.5	62

[a] Experimental conditions: 0.1 mmol BODIPY **4.8a**, aniline **4.20**, 4.5 equivalents $BF_3{\cdot}OEt_2$, 3.6 equivalents *t*-BuONO, reductant, 1 mL solvent, stirring for the indicated time at room temperature. [b] Isolated yield. [c] 3 mL solvent was used. [d] Copper(I) thiophene-2-carboxylate. [e] 3.75 equivalents $BF_3{\cdot}OEt_2$ and 3 equivalents *t*-BuONO were used.

As previously mentioned, DMSO can reduce aryldiazonium salts (section 2). Hence a reductant is not required when DMSO is used as the solvent. The same is true for this nonsequential one-pot procedure. This proved to be a large improvement over the same reaction with ferrocene, providing the desired arylated dye **4.10a** in a good yield of 64% (Table 4.5, entries 3 and 4). However, this yield remains lower than for the reaction between BODIPY **4.8a** and benzenediazonium tetrafluoroborate **4.11a**. Nonetheless, it is a useful procedure because it uses an aromatic amine as the arylating reagent and these reagents are more readily available than the corresponding aryldiazonium salts.

Furthermore, using this one-pot protocol, it is possible to introduce aryl groups onto the BODIPY core for which the required diazonium salt is too unstable to be isolated. An example of this is the diazonium salt of 2-aminobenzothiazole **4.21**. By

reacting 8-(2,6-dichlorophenyl)-BODIPY **4.8a** with excess 2-aminobenzothiazole **4.21** in DMSO in the presence of *tert*-butyl nitrite and boron trifluoride diethyl etherate the corresponding 3,5-bis(benzothiazolyl)-BODIPY **4.23** could be formed after 6 hours in a yield of 13% (Scheme 4.6). However, the major product was the mono derivative **4.22** formed in a yield of 30%. Furthermore, most of the starting dye **4.8a** was recovered after the reaction, indicating that a significant portion of 2-aminobenzothiazole **4.21** did not react with the boron dipyrrin dye **4.8a**. Nonetheless, without this one-pot procedure synthesis of such benzothiazolyl-BODIPYs would require a much longer synthetic route.[20]



Scheme 4.6: Synthesis of benzothiazolyl-BODIPYs using a nonsequential one-pot C–H arylation (Ar = 2,6-dichlorophen-1-yl).

Unfortunately, similar reactions with 2-aminobenzimidazole and 2-aminobenzoxazole were unsuccessful. In the case of 2-aminobenzimidazole no reaction occurred and the starting dye was recovered. In fact, attempts to make and isolate the diazonium salt of 2-aminobenzimidazole resulted in recovery of the aromatic amine. Hence, benzimidazole-2-diazonium was not formed under the used reaction conditions and thus arylation does not take place. On the other hand, reaction between BODIPY **4.8a** and 2-aminobenzoxazole resulted in a complex reaction mixture. The major products in this mixture were identified as monomethyl- and dimethyl-BODIPY dyes, and were probably formed from methyl radicals originating from the DMSO solvent (Chapter 3, section 3).

6. UV-vis spectroscopic properties

Using the developed radical C–H arylation a great variety of aryl groups can easily be introduced onto the BODIPY core. The resulting fluorophore library provides an excellent opportunity to investigate the relationship between the structure and the spectroscopic properties of these dyes. Some of these dyes were previously made

using our direct palladium catalyzed C–H arylation. Their spectroscopic properties have already been discussed in Chapter 1 (Table 1.4 and Table 1.5), so they will not be repeated here. This chapter will instead focus on the new dyes made using our radical C–H arylation (Table 4.6, Table 4.7 and Table 4.8), particularly those containing an aromatic substituent with an electron withdrawing group.

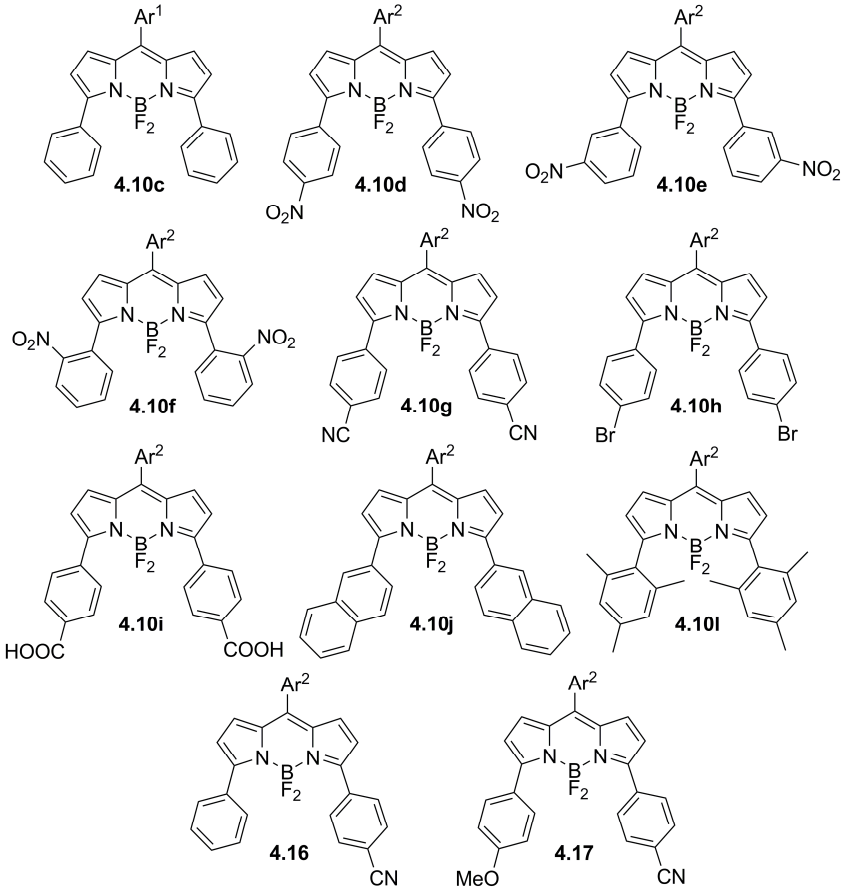


Figure 4.1: Structures of the new 3,5-diaryl-BODIPYs **4.10**, **4.16** and **4.17** for which the spectroscopic properties were measured (Ar_1 = mesityl, Ar_2 = 2,6-dichlorophen-1-yl).

Table 4.6: Spectroscopic data of 3,5-diaryl-BODIPYs **4.10**, **4.16** and **4.17** in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f[e]
4.10c	MeOH	552	582	934	1498	900	0.35[f]
	MeCN	548	582	1051	1619	989	0.54[f]
	EtOAc	553	584	960	1559	944	0.59[f]
	THF	557	586	888	1466	931	0.84
	Toluene	559	589	911	1491	940	0.94
4.10d	MeOH	572	611	1131	1843	1031	0.69
	MeCN	570	613	1217	1850	1053	0.74
	EtOAc	573	613	1139	1768	1017	0.60
	THF	579	617	1079	1799	1038	0.47
	Toluene	579	618	1090	1698	1007	0.68
4.10e	MeOH	559	592	997	1656	959	0.91
	MeCN	558	593	1051	1526	957	0.82[f]
	EtOAc	561	593	955	1680	981	0.87
	THF	564	596	938	1493	986	0.76
	Toluene	568	600	939	1506	986	0.82
4.10f	MeOH	532	559	918	994	-[g]	-[g]
	MeCN	531	554	766	994	-[g]	-[g]
	EtOAc	533	568	1141	1057	1499	0.01[f]
	THF	535	568	1094	1049	-[g]	-[g]
	Toluene	536	575	1258	1008	1441	0.03[f]
4.10g	MeOH	568	602	981	1673	978	0.86
	MeCN	565	602	1081	1819	1007	0.85
	EtOAc	570	604	994	1564	988	0.88
	THF	575	609	957	1570	987	0.67
	Toluene	576	612	1036	1626	1006	0.72
4.10h	MeOH	571	604	950	1587	960	0.86
	MeCN	568	604	1036	1835	1015	0.90
	EtOAc	572	604	926	1547	984	0.88
	THF	577	609	911	1682	1027	0.48
	Toluene	580	612	902	1538	960	0.74

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* rhodamine 6G in ethanol ($\Phi_r = 0.95$) as a reference. [f] Φ_f determined *vs* rhodamine 101 in ethanol ($\Phi_r = 0.96$) as reference instead. [g] Dye is too weakly fluorescent to obtain reliable values.

Table 4.7: Spectroscopic data of 3,5-diaryl-BODIPYs **4.10**, **4.16** and **4.17** in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f[e]
4.10i	MeOH	574	607	954	1638	964	0.79
	MeCN	567	604	1067	1870	1004	0.72
	EtOAc	572	604	913	1457	999	0.83
	THF	577	610	931	1493	997	0.69
	Toluene	-[g]	-[g]	-[g]	-[g]	-[g]	-[g]
	H_2O[h]	565	605	1157	1854	997	0.37[f]
4.10j	MeOH	587	625	1023	1902	1011	0.70
	MeCN	582	626	1208	1895	1047	0.61
	EtOAc	588	626	1032	1829	996	0.54
	THF	593	630	984	1682	1022	0.73
	Toluene	594	632	1006	1670	980	0.56
4.10l	MeOH	-[g]	-[g]	-[g]	-[g]	-[g]	-[g]
	MeCN	525	540	512	802	1136	0.90[f]
	EtOAc	525	541	546	799	1034	0.91[f]
	THF	526	543	604	833	1189	0.82[f]
	Toluene	529	544	530	752	1147	0.98[f]
4.16	MeOH	566	599	973	1586	978	0.94
	MeCN	563	597	1019	1868	1006	0.70
	EtOAc	568	599	911	1575	988	0.86
	THF	573	604	903	1581	975	0.71
	Toluene	574	606	920	1638	992	0.71
4.17	MeOH	582	619	1014	2044	1007	0.50
	MeCN	579	619	1123	2024	1056	0.49
	EtOAc	585	619	947	1996	991	0.52
	THF	590	623	904	1809	1016	0.42
	Toluene	591	625	927	1856	945	0.54

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* rhodamine 6G in ethanol ($\Phi_r = 0.95$) as a reference. [f] Φ_f determined *vs* rhodamine 101 in ethanol ($\Phi_r = 0.96$) as reference instead. [g] Not possible to obtain reliable values due to very limited solubility in the indicated solvent. [h] Aqueous phosphate buffer at pH 7.4.

All synthesized BODIPY dyes are strongly colored solids that form intensely colored solutions with usually bright fluorescence upon irradiation. For the majority of these dyes, their absorption and emission spectra show the typical boron dipyrrin features, being narrow peaks, small Stokes shifts and high fluorescence quantum yields. The visible absorption band is assigned to the strong $S_1 \leftarrow S_0$ transition, while

the much weaker, broad absorption band in the UV spectral range is attributed to the $S_2 \leftarrow S_0$ transition (Figure 4.3). For each dye, the absorption and emission maxima are slightly bathochromically shifted with increasing solvent polarizability. Although the shapes of the spectra of all the investigated difluoroboron dipyrrins are similar, their absorption and emission maxima, Stokes shifts, absorption and emission bandwidths, and fluorescence quantum yields may vary considerably.

Most of the synthesized compounds have high fluorescence quantum yields. This is in part due to restriction of rotation of the 8-(2,6-dichlorophenyl) and 8-mesityl groups by steric hindrance between the chlorine atoms and methyl groups, respectively, and the 1,7-hydrogens of the BODIPY nucleus.[21] The higher fluorescence quantum yields for the diphenyl dye with a *meso*-2,6-dichlorophenyl group **4.10a** (Table 1.5, dye **1.10a**) compared to the derivative with a *meso*-mesityl substituent **4.10c** indicate that the 2,6-dichlorophenyl group is the more efficient rotation-blocking group.

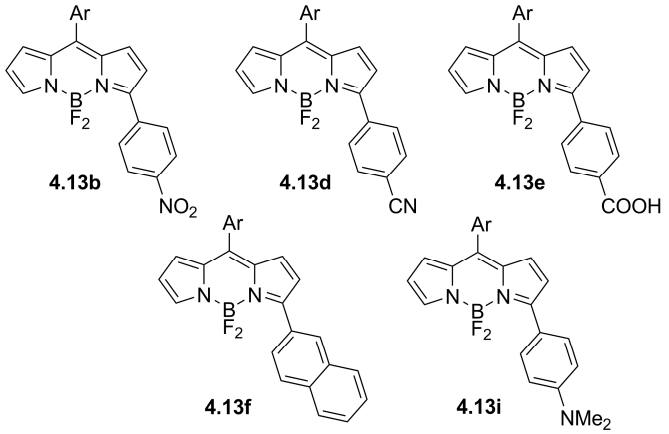


Figure 4.2: Structures of the new 3-monoaryl-BODIPYs **4.13** for which the spectroscopic properties were measured (Ar = 2,6-dichlorophen-1-yl).

Table 4.8: Spectroscopic data of 3-monoaryl-BODIPYs **4.13** in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f[e]
4.13b	MeOH	541	564	754	1648	954	0.63
	MeCN	540	564	788	1578	954	0.93
	EtOAc	543	565	717	1674	922	0.54
	THF	547	569	715	1506	940	0.59
	Toluene	548	573	789	1532	929	0.65
4.13d	MeOH	539	559	681	1405	890	0.94
	MeCN	537	560	749	1410	907	0.79
	EtOAc	541	561	651	1432	889	0.66
	THF	544	565	668	1305	878	0.72
	Toluene	546	568	709	1363	926	0.73
4.13e	MeOH	542	561	633	1389	899	0.85
	MeCN	539	559	656	1405	924	0.84
	EtOAc	542	561	625	1319	917	0.85
	THF	545	566	673	1263	906	0.35
	Toluene	548	568	667	1390	924	0.74
	H_2O[h]	536	560	800	1569	969	0.85
4.13f	MeOH	549	572	740	1600	972	0.64
	MeCN	547	572	799	1612	1022	0.77
	EtOAc	551	573	704	1704	1114	0.78
	THF	554	576	682	1360	946	0.75[f]
	Toluene	557	580	697	1482	964	1.00[f]
4.13i	MeOH	608	-[g]	-[g]	2344	-[g]	-[g]
	MeOH[i] + H^+	535	554	641	1382	927	0.54
	MeCN	608	-[g]	-[g]	3483	-[g]	-[g]
	EtOAc	608	-[g]	-[g]	2255	-[g]	-[g]
	THF	612	629	449	2232	1229	0.09[f]
	Toluene	619	665	1123	2154	1510	0.16[f]

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* rhodamine 101 in ethanol (Φ_r = 0.96) as a reference. [f] Φ_f determined *vs* rhodamine 6G in ethanol (Φ_r = 0.95) as reference instead. [g] Dye is not fluorescent. [h] Aqueous phosphate buffer at pH 7.4. [i] Methanol with excess $HClO_4$ was used.

The 3,5-diarylated dyes **4.10** have bathochromically shifted absorption and emission spectra compared to their 3-monoarylated counterparts **4.13**, whom themselves posses a red-shifted spectra compared to the unsubstituted starting material **4.8** (Table 4.6, Table 4.7, Table 4.8 and Figure 4.3). These shifts reflect the better π-conjugation in dyes with aryl groups on their 3,5-positions (General introduction, section 4). As mentioned earlier, placing one phenyl group at the 3-position (in **4.13a**) produces a bathochromic shift of approximately 29 nm in absorption and 35 nm in emission compared to the starting compound **4.8**. Incorporating a second phenyl group (in **4.10a**) entails an additional red shift of approximately 27 nm in absorption and 40 nm in emission relative to the mono-phenyl dye **4.13a** (Chapter 1, section 5). The absorption and emission maxima of the mono- and di(2-naphthyl) substituted fluorophores (**4.13f** and **4.10j**) are bathochromically shifted compared to those of the corresponding phenyl substituted analogues (**4.13a** and **4.10a**). This reflects the longer conjugation length in the 2-naphthyl substituted derivatives relative to their phenyl counterparts.

Replacing the 3,5-phenyl substituents by electron-donating groups results in a larger red-shift in the spectra of both the mono- and diarylated compounds (Chapter 1, section 5). In contrast, the bulky mesityl group (in **4.10l**) introduces only a small bathochromic shift, suggesting a severely restricted electronic coupling caused by steric hindrance twisting the mesityl group out of the BODIPY plane. Furthermore, this 3,5-dimesityl dye **4.10l** has very small Stokes shifts, combined with high fluorescence quantum yields, suggesting a very rigid structure. The strongly electron donating substituent in 3-(4-(dimethylamino)phenyl)-BODIPY **4.13i** creates a very large red-shift, however this dye shows no fluorescence in more polar solvents. The fluorescence of this dye is quenched by the electron-rich 3-(4-(dimethylamino)-phenyl) substituent. Addition of acid blocks the lone electron pair of the nitrogen donor and hence decreases the electron-donating ability of the amine. This leads to inhibition of the quenching process, resulting in a “switching on” of the fluorescence, which renders this molecule an extremely sensitive probe for pH. Furthermore, protonation of the nitrogen donor induces a hypsochromic shift in the spectra of this chromophore **4.13i**.

BODIPY dyes with aryl substituents bearing an electron withdrawing group (such as 4-nitrophenyl, 4-cyanophenyl, 4-bromophenyl and 4-carboxyphenyl) show smaller bathochromic spectral shifts than the corresponding phenyl derivatives (**4.10a** and **4.13a**), but the influence on the fluorescence quantum yields is minimal. This effect is seen for both mono- and diarylated dyes. The 3,5-di(4-nitrophenyl) substituted fluorophore **4.10d** shows rather small bathochromic shifts compared to the 3,5-di(3-nitrophenyl) derivative **4.10e**, but shows much larger red shifts compared to the 3,5-di(2-nitrophenyl) compound **4.10f**. The quantum yields and Stokes shifts of the 4-nitro **4.10d** and 3-nitro **4.10e** dyes are comparable, whereas the sterically hindered 2-nitro variant **4.10f** barely shows any fluorescence. Negligible fluorescence has previously also been observed for a 8-(4-nitrophenyl)-3-phenyl-BODIPY and a 8-(4-nitrophenyl)-3,5-diphenyl-BODIPY (Chapter 1, section 5).[22] Both mono(4-carboxyphenyl) **4.13e** and di(4-carboxyphenyl) **4.10i** substituted dyes are soluble in slightly basic water. Combined with their moderate to good quantum yields of fluorescence (up to 0.85), makes these compounds promising starting points for constructing labeling dyes.

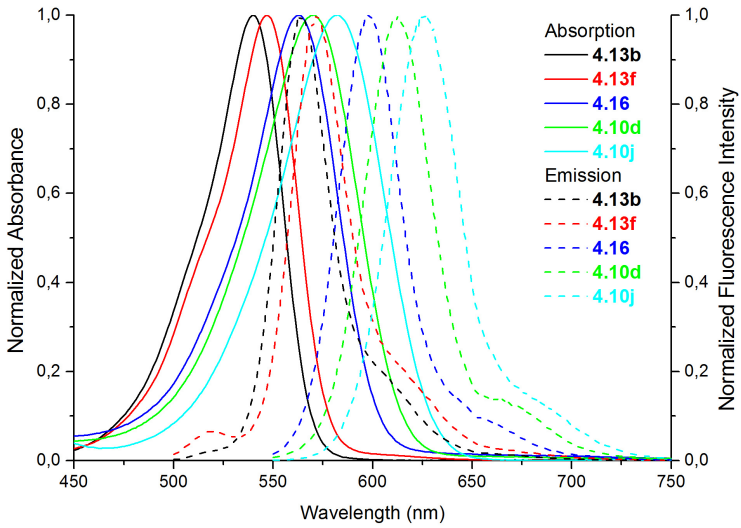


Figure 4.3: Normalized, visible absorption spectra and corresponding normalized fluorescence emission spectra of a selection of *meso*-(2,6-dichlorophenyl) substituted BODIPY dyes (**4.13b**, **4.13f**, **4.16**, **4.10d**, **4.10j**) in MeCN.

The absorption and emission maxima of the two asymmetrically arylated dyes (**4.16** and **4.17**) are the average of those of their corresponding symmetrical analogues. The spectral maxima of 3-(4-cyanophenyl)-5-phenyl-BODIPY **4.16** are the average of the 3,5-diphenyl **4.10a** and the 3,5-di(4-cyanophenyl) **4.10g** fluorophores, whereas those of 3-(4-cyanophenyl)-5-(4-methoxyphenyl)-BODIPY **4.17** are the average of the 3,5-di(4-cyanophenyl) **4.10g** and the 3,5-di(4-methoxyphenyl) **4.10m** dyes.

As mentioned earlier, annulated dyes possess larger red-shifts than the corresponding arylated dyes due to a more effective conjugation. A preliminary spectroscopic study of bis(biphenyl)-fused BODIPY **4.18** in THF showed that annulation indeed created a very large red-shift. The absorption maximum of this annulated dye in THF is located at 692 nm, while the emission maximum in the same solvent is situated at 725 nm. Hence, radical C–H arylation with biphenyl-2-diazonium tetrafluoroborate **4.11k** followed by oxidative cyclization afforded a very large bathochromic shift of about 200 nm compared to the starting compound **4.8**.

7. Conclusion

A versatile, general method for the synthesis of brightly fluorescent 3,5-diarylated and 3-monoarylated BODIPY dyes has been developed and investigated. This method is based on a ferrocene catalyzed reduction of aryldiazonium salts in the presence of a boron dipyrromethene dye and is a fast and high yielding reaction displaying a broad scope. In this way a great variety of aryl substituents can easily and selectively be introduced onto the 3,5-positions of BODIPY without needing a tedious synthesis of substituted pyrrole building blocks, unstable intermediates or harsh reaction conditions. This radical arylation has also been modified to allow a one-pot procedure using aromatic amines as the arylating reagents, which is a useful strategy for aromatic amines for which the corresponding aryldiazonium salt cannot be isolated.

All these advantageous properties make that this radical C–H arylation is an interesting strategy to synthesize fluorophores whose absorption and emission spectra are bathochromically shifted compared to those of their starting boron dipyrrins. Furthermore, complex dyes, such as asymmetrically arylated dyes and annulated

fluorophores, are readily accessible from simple 3,5-unsubstituted BODIPYs using the developed radical arylation. In other words, this new transformation is a powerful tool for synthesizing novel red-shifted boron dipyrromethene fluorophores.

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Chapter 5. Radical C–H alkylation of BODIPY dyes using potassium trifluoroborates or boronic acids

Part of this chapter is based on:

B. Verbelen, L. C. D. Rezende, S. Boodts, J. Jacobs, L. Van Meervelt, J. Hofkens, W. Dehaen, *Chem. Eur. J.* **2015**, *21*, 12667–12675.

1. Introduction

Most reactions to functionalize BODIPY fluorophores reported so far are arylation, alkenylation or alkynylation reactions. Up to this point, only three alkylation reactions have been described. The first two alkylation reactions are both nucleophilic substitutions of hydrogen using carbon nucleophiles.[1] While these methods use relatively mild conditions, their scope is rather limited as only enolates can react in this type of transformations. The last reported alkylation reaction uses a Negishi reaction between organozinc reagents and halogenated boron dipyrromethenes to introduce simple primary alkyl groups.[2] In the case of secondary alkyl groups, isomerization occurred to form a mixture of compounds. Further disadvantages of this alkylation method are the need for dry reaction conditions and the use of halogenated boron dipyrrins, which require extra steps and unstable halogenated pyrrole intermediates (General introduction, section 3).

A more general and straightforward alkylation of BODIPY dyes could be possible with a radical C–H alkylation reaction (Chapter 3). As mentioned earlier, to allow a successful radical substitution of the BODIPY core the desired radical should be formed without relying on a radical chain process (Chapter 3). Direct formation of the required radical has been successfully applied in the development of a radical C–H arylation using aryldiazonium salts (Chapter 4),[3] illustrating this principle.

Other possible radical precursors are boronic acids as well as potassium trifluoroborates. Both compounds are known to decompose into radicals through a single-electron transfer in the presence of an oxidant.[4,5] Hence, oxidation of alkylboronic acids or potassium alkyltrifluoroborates forms alkyl radicals, and this could prove to be an interesting method to alkylate boron dipyrromethenes. Herein,

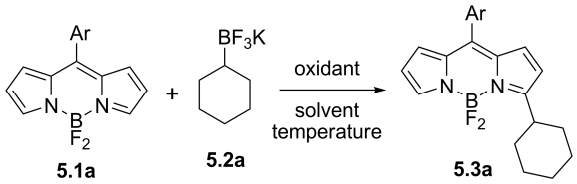
we report our investigation on the use of stoichiometric alkylboronic acids and potassium alkyltrifluoroborates as radical precursors in a direct C–H alkylation of readily available *meso*-substituted BODIPY dyes **5.1**.

2. Optimization of the reaction

A well-known example of a single-electron oxidant in the field of radical chemistry is manganese(III) acetate.[6] Hence, this salt is often used for the oxidation of boronic acids and potassium trifluoroborates in order to generate radicals. This oxidant was consequently used for a trial reaction between 8-(2,6-dichlorophenyl)-BODIPY **5.1a** and cyclohexylboronic acid **5.2d**. Cyclohexylation was chosen due to the combination of commercial availability of the starting compound and ease of purification of the desired product. This reaction was carried out in 1,2-dichloroethane at 50 °C, but unfortunately after 2 days only a trace amount of product was formed. Perhaps oxidation of the boronic acid was under these conditions inefficient. On the other hand, the more electron-rich potassium cyclohexyltrifluoroborate **5.2a** (Table 5.1, entry 1) resulted in a more efficient formation of cyclohexyl radicals under the same reaction conditions. Hence, the desired cyclohexyl-BODIPY **5.3a** was, to our delight, formed in a good yield of 52% after reacting 45 hours at 50 °C.

Characterization of the alkylated product **5.3a** formed in this reaction revealed that the cyclohexyl radical reacted exclusively at the 3-position of the BODIPY core. Such a high regioselectivity for radical reactions on boron dipyrromethenes has been demonstrated before with our radical C–H arylation (Chapter 4).[3] This was explained using the strongly polarizing effect the BF_2-group has on the dipyrromethene core. Furthermore, during this radical alkylation only a trace amount of the 3,5-dialkylated product **5.4** was formed, demonstrating the very good selectivity of mono- over difunctionalization for this radical C–H reaction.

Table 5.1: Optimization of radical C–H alkylation of *meso*-substituted BODIPY **5.1a** using potassium cyclohexyltrifluoroborate **5.2a** (Ar = 2,6-dichlorophen-1-yl).[a]



5.1a **5.2a** **5.3a**

Entry	Oxidant	Solvent	T (°C)	Reaction time	Yield (%)[b]
1	$Mn(OAc)_3 \cdot 2H_2O$	1,2-dichloroethane	50	45 h	52
2[c]	$Mn(OAc)_3 \cdot 2H_2O$	DMF	50	23 h	77
3	$Mn(OAc)_3 \cdot 2H_2O$	acetone	50	22.5 h	35
4	$Mn(OAc)_3 \cdot 2H_2O$	DMSO	50	23 h	30
5	$Mn(OAc)_3 \cdot 2H_2O$	MeOH	50	22 h	40
6	$Mn(OAc)_3 \cdot 2H_2O$	toluene	50	19 h	18
7	$K_2Cr_2O_7$	DMF	50	4 days	28
8	$CuCl_2$	DMF	50	4 days	trace
9	$Ce(NH_4)_4(SO_4)_4 \cdot 2H_2O$	DMF	50	4 days	trace
10	*p*-chloranil	DMF	50	19 h	-[d]
11[e]	$Mn(OAc)_3 \cdot 2H_2O$	DMF	50	24.5 h	46
12	$Mn(OAc)_3 \cdot 2H_2O$	DMF	rt	46 h	36
13	$Mn(OAc)_3 \cdot 2H_2O$	DMF	80	4.5 h	68[f]

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophenyl)-BODIPY **5.1a**, 1 equivalent potassium cyclohexyltrifluoroborate **5.2a**, 2.5 equivalents oxidant, 1 ml of solvent, stirring for the indicated time at the indicated temperature. [b] All yields are isolated yields. [c] Highest yielding conditions. [d] No reaction occurred. [e] 1 equivalent of oxidant was used. [f] 21 % dicyclohexylated side-product **5.4** was also isolated.

To further improve the yield, the alkylation reaction was tested in various solvents (Table 5.1, entries 1-6), using different oxidants (Table 5.1, entries 7-10) and using different amounts of oxidant (Table 5.1, entry 11). The reaction in DMF using 2.5 equivalents of manganese(III) acetate resulted in the highest yield, providing the desired 3-cyclohexyl-BODIPY **5.3a** in an excellent yield of 77% after 23 hours (Table 5.1, entry 2). Using a slight excess of trifluoroborate resulted in an identical yield. The effect of temperature was also investigated. At room temperature, instead of 50 °C, the cyclohexyl-product **5.3a** was isolated in a lower yield after a longer reaction time (Table 5.1, entry 12), after 46 hours a substantial amount of starting material was still present in the crude mixture. On the other hand, at 80 °C the

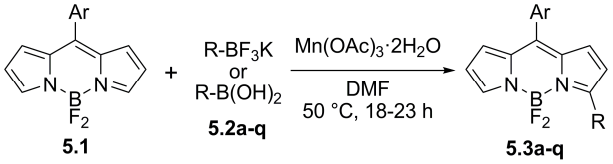
reaction was completed within a few hours (Table 5.1, entry 13). However, at this higher temperature dialkylation became significant, providing 3,5-dicyclohexyl-BODIPY **5.4** in 21% yield as a side-product, which reduced the monoalkylation yield.

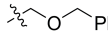
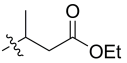
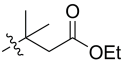
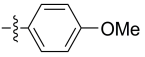
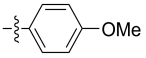
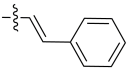
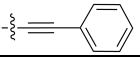
3. Scope of the reaction

Knowing the optimal conditions, the scope of this radical C–H transformation was investigated by executing this reaction with different BODIPY substrates and a range of trifluoroborates (Table 5.2). Different *meso*-substituted boron dipyrromethenes **5.1a-e** could be cyclohexylated providing the alkylated product **5.3a-e** in a good to excellent yield (Table 5.2, entries 1-5). Noteworthy is the product formed from *meso*-(methylthio)-BODIPY **5.1e**, as its thioether substituent provides an opportunity to further functionalize this alkylated dye (General introduction, section 3.2.2).

Not only cyclohexylation is possible, both tertiary and acyclic secondary alkyltrifluoroborates were reactive under these conditions, producing 3-*tert*-butyl-BODIPY **5.3g** (Table 5.2, entry 7) and 3-*sec*-butyl-BODIPY **5.3h** (Table 5.2, entry 8) in a straightforward fashion in similar yields. Unfortunately, a primary organoboron compound, such as potassium octyltrifluoroborate **5.2i** (Table 5.2, entry 9), did not give the expected product using these reaction conditions. Only a trace amount of the desired 3-octyl-boron dipyrrin **5.3i** was detected. Such a low reactivity of primary alkyltrifluoroborates in this type of reactions has been described before.[5b] This can be attributed to a more difficult oxidation of primary organoboron compounds compared to secondary and tertiary derivatives. Hence, if an electron-donating group is present to increase the electron density of the α-carbon bearing the trifluoroborate group, such a limited formation of the alkyl radical through oxidation should not be a problem. Indeed, use of potassium benzyloxymethyltrifluoroborate **5.2j** resulted in the formation of the expected 3-(benzyloxymethyl)-BODIPY dye **5.3j** (Table 5.2, entry 10). To our regret, this alkylated fluorophore proved to be unstable under the used reaction conditions and was lost during the reaction.

Table 5.2: Scope of radical C–H functionalization of BODIPY fluorophores using potassium trifluoroborates and boronic acids.[a]



Entry	Compound	Ar	R	Reaction time (h)	Yield (%)[b]
1	**a**	2,6-Dichlorophenyl		23	77
2	**b**	Phenyl		19	60
3	**c**	Mesityl		19.5	50
4	**d**	4-Nitrophenyl		18.5	58
5	**e**	Methylthio		18.5	44
6[c]	**f**	2,6-Dichlorophenyl		20	67
7	**g**	2,6-Dichlorophenyl		19	60
8	**h**	2,6-Dichlorophenyl		19	76
9	**i**	2,6-Dichlorophenyl		20	trace[d]
10	**j**	2,6-Dichlorophenyl		18	-[e]
11	**k**	2,6-Dichlorophenyl		20	51
12	**l**	2,6-Dichlorophenyl		18.5	57
13	**m**	2,6-Dichlorophenyl		22.5	42
14	**n**	2,6-Dichlorophenyl		18	42
15[c]	**o**	2,6-Dichlorophenyl		20	34
16	**p**	2,6-Dichlorophenyl		19	20
17	**q**	2,6-Dichlorophenyl		19	-[f]

[a] Experimental conditions: 0.1 mmol BODIPY **5.1**, 1 equivalent potassium alkyltrifluoroborate **5.2**, 2.5 equivalents $Mn(OAc)_3 \cdot 2H_2O$, 1 ml DMF, stirring for the indicated time at 50 °C. [b] Isolated yield. [c] Corresponding boronic acid was used instead of the potassium trifluoroborate. [d] Formation of alkylated product has been observed *via* mass spectrometry (EI mode). [e] Product was formed, as detected *via* mass spectrometry (EI mode), but was not stable under the reaction conditions and decomposed. [f] No reaction occurred.

The scope of this radical transformation is not limited to simple unfunctionalized alkyl groups, as trifluoroborates bearing an ester group (**5.2k** and **5.2l**) reacted to form ester functionalized BODIPY dyes (**5.3k** and **5.3l**) in a good yield (Table 5.2, entries 11 and 12). These experiments illustrate the generality of this radical C–H reaction. Comparing these results with other reported alkylation reactions of boron dipyrromethenes,[1,2] it becomes apparent that this radical alkylation possess a significantly broader scope. Thus a great variety of alkylated BODIPY fluorophores can be synthesized using a simple protocol without the need for reactive boron dipyrrin derivatives.

Potassium alkyltrifluoroborates are not the only known type of trifluoroborates. Aryl, alkenyl and alkynyl derivatives can also be prepared. Subsequently, the reactivity of these substrates under the optimized conditions was investigated. Using potassium aryltrifluoroborates **5.2m-n** the corresponding 3-aryl-BODIPYs **5.3m-n** could be synthesized in a moderate yield (Table 5.2, entries 13 and 14). These yields are not competitive with those obtained with our previously reported C–H arylation methodology (Chapter 4),[3] although this reaction could still prove to be a useful alternative. Also in the case of potassium trans-β-styryltrifluoroborate **5.2p** a reaction was observed. Unfortunately, due to the radical nature of the reaction, isomerization of the double bond takes place. Accordingly, a mixture of *cis*- and *trans*-3-styryl-BODIPY was isolated in 39% yield, with a *cis*/*trans* ratio of 16/84. After crystallization of this mixture, pure trans-3-styryl-BODIPY **5.3p** was obtained in a yield of 20% (Table 5.2, entry 14). Thus, this radical alkenylation is not very effective compared to the previously reported direct alkenylation procedure using a nitro-styrene.[1b] Lastly, the reactivity of potassium (phenylethynyl)trifluoroborate **5.2q** was tested, but regrettably no C–H alkynylation reaction took place (Table 5.2, entry 17).

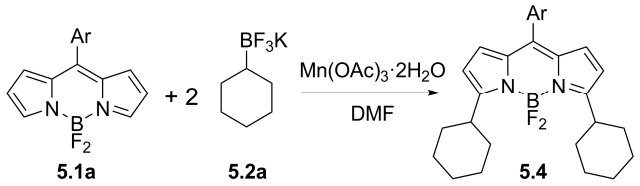
Due to the greater availability of boronic acids, we wanted to revisit their application under our optimized conditions. Hence, use of boronic acids as the radical precursor for the functionalization of boron dipyrrins was once more tested. To our delight, in DMF the use of cyclohexylboronic acid **5.2f** resulted in the formation of

the desired 3 cyclohexyl-BODIPY **5.3f** in a good yield (Table 5.2, entry 6). However, the resulting yield was 10% lower than when potassium cyclohexyltrifluoroborate **5.2a** was used. This lower yield is presumably due to the less efficient oxidation of a boronic acid compared to a more electron-rich trifluoroborate, as described above. Similarly, using 4-methoxyphenylboronic acid **5.2o** the corresponding 4-methoxyphenyl-BODIPY **5.3o** could be synthesized in an 8% lower yield than the trifluoroborate example (Table 5.2, entry 14 and 15). Lastly, the pinacol ester of cyclohexylboronic acid was investigated as a radical source under our optimized conditions, unfortunately after 42 hours only a trace amount of the 3-cyclohexyl-BODIPY **5.3f** was formed.

4. Extension to di-, tri- and tetraalkylation

As observed when studying the effect of temperature on the radical monoalkylation reaction (section 2), dialkylation became significant at a higher temperature. Consequently, at this temperature the reaction was no longer selective for monoalkylation. Accordingly, it was investigated if this radical reaction could be modified to allow dialkylation using 2 equivalents of potassium cyclohexyltrifluoroborate **5.2a** to effectively synthesize 3,5-dicyclohexyl-BODIPY **5.4**. To this end, the C–H dialkylation reaction was executed at higher temperatures (Table 5.3). As the temperature increased, the reaction time decreased and the yield of the dicyclohexyl product **5.4** increased. At 80 °C the reaction is completed after 2 hours providing the 3,5-dicyclohexyl fluorophore **5.4** in an excellent yield of 92% (Table 5.3, entry 4). However, at even higher temperatures decomposition of the starting compound **5.1a** became problematic causing an *in situ* excess of trifluoroborate **5.2a** and hence a significant formation of tricyclohexyl-BODIPY **5.5**. This combined with a rather difficult separation, due to the extra side products being formed in this case, resulted in a drastically lower yield when the reaction was done at 90 °C (Table 5.3, entry 5).

Table 5.3: Optimization of radical C–H dialkylation of BODIPY **5.1a** using potassium cyclohexyltrifluoroborate **5.2a** (Ar = 2,6-dichlorophen-1-yl).[a]

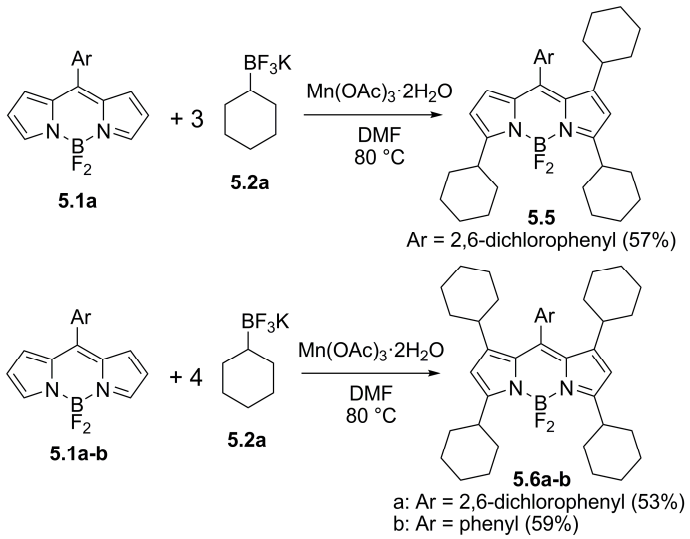


Entry	T (°C)	Reaction time	Dialkylation yield (%)[b]
1	50	45 h	23
2	60	44 h	64
3	70	21 h	86
4[c]	80	2 h	92
5	90	45 min	14

[a] Experimental conditions: 0.1 mmol 8-(2,6-dichlorophenyl)-BODIPY **5.1a**, 2 equivalents potassium cyclohexyltrifluoroborate **5.2a**, 5 equivalents $Mn(OAc)_3 \cdot 2H_2O$, 1 ml DMF, stirring for the indicated time at the indicated temperature. [b] All yields are isolated yields. [c] Highest yielding conditions.

When the dialkylation reaction was done at 80 °C (Table 5.3, entry 4), trace amounts of tricyclohexyl-BODIPY **5.5** and tetracyclohexyl-BODIPY **5.6a** were formed as well as the main dicyclohexyl product **5.4**. At 90 °C an even higher amount of tri- and tetracyclohexylated dyes were formed, however the increased decomposition and side-product formation in this case made complete purification of these products not possible. Still, by using a higher amount of potassium cyclohexyltrifluoroborate **5.2a** the reaction at 80 °C could be modified to allow further alkylation of the boron dipyrromethene core (Scheme 5.1). Thus, reaction of 8-(2,6-dichlorophenyl)-BODIPY **5.1a** with 3 equivalents of the organoboron compound **5.2a** resulted in the formation of 1,3,5-tricyclohexyl-BODIPY **5.5** in a yield of 57%. On the other hand, using 4.5 equivalents of the same trifluoroborate **5.2a** gave 53% of 1,3,5,7-tetracyclohexyl-BODIPY **5.6a**. Similarly, 8-phenyl-BODIPY **5.1b** could be tetraalkylated in a comparable yield. It should be mentioned that the tetracyclohexylation of 8-phenyl-BODIPY **5.1b** was significantly faster than the reaction of the more sterically hindered 8-(2,6-dichlorophenyl) derivative **5.1a**, with the reaction being completed in 3.5 hours for the 8-phenyl dye **5.1b** and in 19.5 hours for the dichlorophenyl dye **5.1a**. Hence, this radical transformation allows the

synthesis of boron dipyrrin dyes with multiple *sec*-alkyl substituents, such as 1,3,5,7-tetracyclohexyl-BODIPYs **5.6**. These are compounds for which the synthesis has not been described before.



Scheme 5.1: Tri- and tetraalkylation of *meso*-substituted BODIPY dyes **5.1** using an excess of potassium cyclohexyltrifluoroborate **5.2a** at higher temperatures.

Characterization of the formed 1,3,5,7-tetracyclohexyl-BODIPY **5.6a** using X-ray diffraction showed that cyclohexyl groups are indeed located at the 1,3,5- and 7-positions of the BODIPY core (Figure 5.1). Inside the crystal packing, dichloromethane is located in a void of 17.8 $Å^3$, between four boron dipyrrin molecules. The particular location of the dichloromethane and the effect of the bulky cyclohexyl substituents make it impossible for these BODIPY molecules to form π–stacking interactions between each other, thus limiting aggregation-induced fluorescence quenching. This reduced quenching is apparent from the fluorescent behavior of this compound **5.6a** in the solid state (section 6). In contrast, π–stacking is clearly observed in boron dipyrromethenes lacking bulky substituents, resulting in a quenching of the solid-state fluorescence.[7]

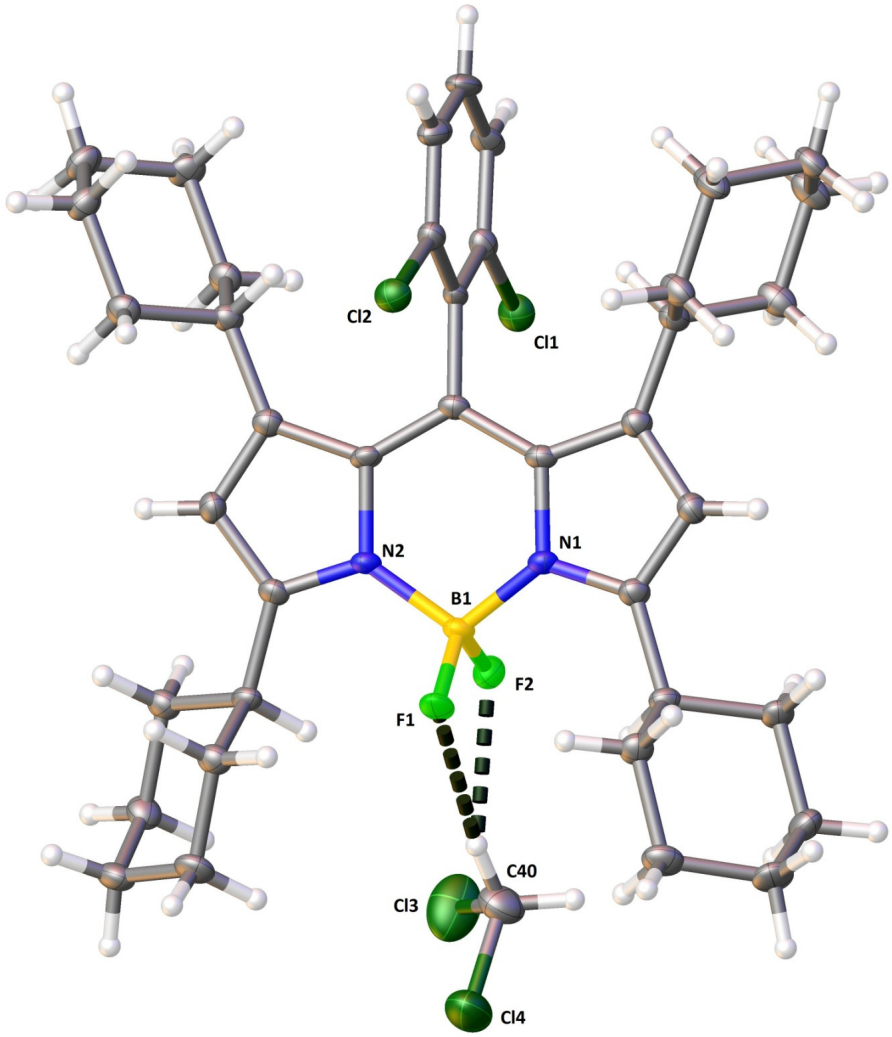
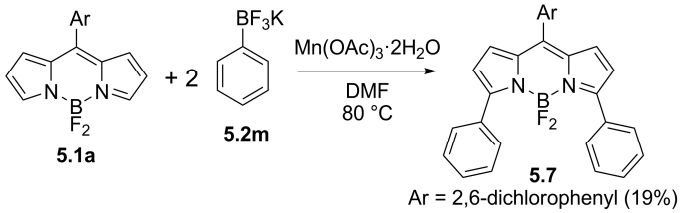


Figure 5.1: The molecular structure of 1,3,5,7-tetracyclohexyl-BODIPY **5.6a** as determined *via* X-ray diffraction.

As mentioned before, alkyl radicals reacted exclusively at the 3-positions of a *meso*-substituted dye **5.1** at 50 °C. By using an excess of potassium cyclohexyltrifluoroborate **5.2a** at 80 °C, the 1,3,5,7-positions can also be substituted. However, no reaction of this bulky radical was observed on the 2,6-positions. In order to investigate if the 2,6- or 8-positions are at all reactive towards alkyl radicals,

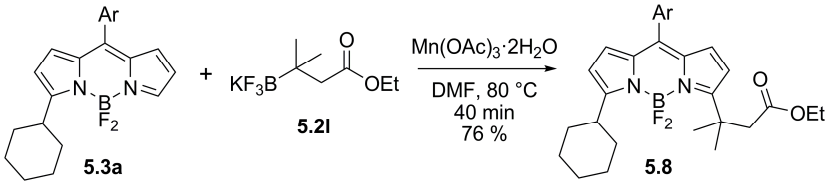
the less sterically hindered 1,3,5,7-tetramethyl-BODIPY was subjected to the developed radical alkylation conditions with potassium cyclohexyltrifluoroborate **5.2a**. Despite that the 2,6- and 8-positions are unsubstituted in this molecule, no reaction was observed and the starting material was recovered. This once more illustrates the high selectivity of this radical reaction.

Difunctionalization at higher temperatures could also be applied for the radical C–H arylation using 2 equivalents of potassium phenyltrifluoroborates **5.2m** at 80 °C. In this way, 3,5-diphenyl-BODIPY **5.7** was synthesized in an admittedly low yield (Scheme 5.2). This once more indicates the superiority of our previous radical arylation method (Chapter 4),[3] at least in the case of direct arylation. Using an excess of 4.5 equivalents of organoboron compound **5.2m** did not improve this yield, neither was the formation of tri- or tetraarylated dyes detected.



Scheme 5.2: Diarylation of 8-(2,6-dichlorophenyl)-BODIPY **5.1a** using an excess of potassium phenyltrifluoroborates **5.2m**.

Lastly, the increased reactivity at higher temperatures can also be exploited to allow the synthesis of an asymmetric dye bearing two different alkyl groups. When 3-cyclohexyl-BODIPY **5.3a** was reacted with 1 equivalent of ester functionalized trifluoroborate **5.2l** at 80 °C for 40 minutes, the desired asymmetrically substituted fluorophore **5.8** was isolated in an excellent yield of 76% (Scheme 3). The synthesis of such an asymmetrically dialkylated derivative bearing a functional group would be rather difficult with previously reported methodologies. Hence, this example illustrates the potential of this novel radical C–H alkylation reaction, as it allows the synthesis of sophisticated dyes using a simple, straightforward procedure.



Scheme 5.3: Synthesis of an asymmetrically alkylated BODIPY fluorophore **5.8** (Ar = 2,6-dichlorophen-1-yl).

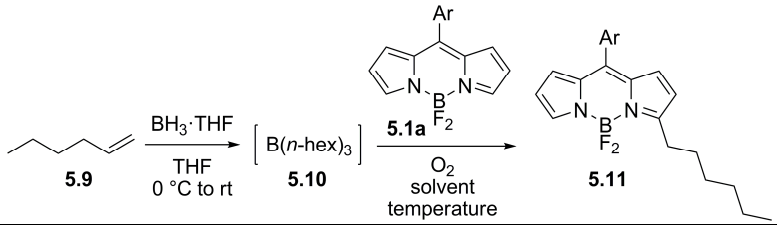
5. Radical C-H alkylation using *in situ* generated trialkylboranes

The lack of reactivity of primary alkyl trifluoroborates is presumably due to their difficult oxidation by manganese(III) acetate compared to the more electron-rich secondary and tertiary derivatives. By using a more electron-rich boron compound, than a trifluoroborate or a boronic acid, reaction with a primary alkyl substituent might still be possible. For example, trialkylboranes readily react with oxygen, even at low temperatures, forming alkyl radicals.[8] In fact, oxidation of triethylborane by air is a common initiation system for radical chain reactions. As mentioned before, using this initiator at room temperature to functionalize BODIPY with a xanthate resulted in formation of 3-ethyl and 3,5-diethyl dyes rather than the desired compound (Chapter 3). This indicates that functionalizing boron dipyrromethenes through oxidation of primary trialkylboranes with oxygen is indeed possible. The feasibility of this radical alkylation was therefore further investigated.

As trialkylboranes react with air,[8] it is the most convenient to prepare these compounds just before use *via* a hydroboration of an alkene in THF with borane tetrahydrofuran.[9] 1-Hexene **5.9** was chosen as the alkene to form trihexylborane **5.10**, which was tested as a reagent to introduce a primary hexyl group onto the BODIPY core. For the initial experiment, a DMF solution of 8-(2,6-dichlorophenyl)-BODIPY **5.1a** was added to the reaction mixture after trihexylborane **5.10** was formed. DMF was used for this trial reaction, because this solvent gave the highest yield for radical alkylation of boron dipyrrins with a potassium trifluoroborate (section 2). Oxidation of the *in situ* formed trihexylborane **5.10** was achieved by stirring the reaction under an oxygen atmosphere at room temperature. After 19 hours the desired 3-hexyl dye **5.11** was isolated in a low yield of 13% (Table 5.4, entry 1). Hence, oxidation of an

in situ generated primary trialkylborane is a possible strategy to make a primary alkyl substituted BODIPY dye.

Table 5.4: Optimization of radical C–H alkylation of *meso*-substituted BODIPY **5.1a** using *in situ* generated trihexylborane **5.10** (Ar = 2,6-dichlorophen-1-yl).[a,b]



Entry	Amount of 1-hexene	Administration method of O_2	Solvent	T (°C)	Time (h)	Yield (%)[c]
1[d]	3 eq	O_2 atmosphere	DMF	rt	19	13
2	3 eq	air atmosphere	DMF	rt	21	17
3	3 eq	bubbling O_2	DMF	rt	4.5	15
4	3 eq	bubbling air	DMF	rt	4.5	27
5	3 eq	bubbling air	DMF	0	4.5	28
6	3 eq	bubbling air	DMF	50	4	16
7	3 eq	bubbling air	dry DMF	rt	4.5	18
8	3 eq	bubbling air	THF	rt	4	trace
9	3 eq	bubbling air	DCM	rt	4	trace
10	3 eq	bubbling air	DMSO	rt	4.5	26[e]
11	3 eq	bubbling air	toluene	rt	4	trace
12	3 eq	bubbling air	1-butanol	rt	4	trace
13	3 eq	bubbling air	DMA	rt	4	18
14	3 eq	bubbling air	1,4-dioxane	rt	4	trace
15	1 eq	bubbling air	DMSO	rt	4	20
16	6 eq	bubbling air	DMSO	rt	4	26
17[f]	1 eq	bubbling air	DMSO	rt	4	9

[a] All reactions were done on a 0.1 mmol scale. [b] Experimental conditions for step 1: 1-hexene **5.9**, 0.1 mL dry THF, N_2 atmosphere, BH_3·THF (1/3 equivalents of 1-hexene) at room temperature for one hour. Experimental conditions for step 2: add 0.1 mmol 8-(2,6-dichlorophenyl)-BODIPY **5.1a**, 0.9 mL solvent, O_2, stirring for the indicated time at the indicated temperature. [c] All yields are isolated yields. [d] The first step (synthesis trihexylborane) had reacted for 3 hours. [e] Less side products were formed during the reaction resulting in an easier purification. [f] 9-BBN was used instead of BH_3·THF.

To improve the yield of this transformation different reaction conditions were tried for the oxidation step. Stirring the reaction under air instead of an oxygen atmosphere resulted in a slightly better yield (Table 5.4, entry 2). While bubbling oxygen through

the solution during the reaction gave a similar yield (Table 5.4, entry 3), doing the same with air provided a larger amount of 3-hexyl product **5.11** (Table 5.4, entry 4). Investigating the influence of temperature (Table 5.4, entries 5 and 6) revealed that a higher temperature resulted in a lower yield, while reacting at 0 °C gave a similar result as the reaction at room temperature. Several solvents were also tested for the oxidation step (Table 5.4, entries 7-14) of which only DMF, DMA and DMSO gave more than a trace amount of product. The reaction in DMSO resulted in a similar yield as the one in DMF, however less side products were formed in DMSO. Hence, DMSO was used as the solvent for subsequent reactions. Lowering the amount of formed trialkylborane **5.10**, by lowering the amount of used 1-hexene and borane tetrahydrofuran, gave a lower yield (Table 5.4, entry 15). On the other hand, increasing this amount did not provide an improvement (Table 5.4, entry 16). Lastly, 9-BBN was tried as an alternative for borane tetrahydrofuran[8] (Table 5.4, entry 17), however 9-BBN proved to be an inferior reagent for this transformation.

Unfortunately, even with the best conditions (Table 5.4, entry 10) the desired 3-hexyl-BODIPY **5.11** was formed in only a moderate yield of 26%. In order to better compare this radical reaction with C–H alkylation using a potassium trifluoroborate, the same procedure was used for the reaction between *meso*-(2,6-dichlorophenyl)-BODIPY **5.1a** and cyclohexene. This provided the cyclohexylated dye **5.3a** in 27%, a significant lower yield than for the same reaction using potassium cyclohexyltrifluoroborate **5.2a**. Despite the lower yields, this reaction using *in situ* formed trialkylboranes could still be useful as it provides access to primary alkyl substituted BODIPY dyes that are unavailable using trifluoroborates.

6. UV-vis spectroscopic properties

The spectroscopic properties of newly synthesized compounds were studied in five solvents and overall typical BODIPY features were observed (Table 5.5, Table 5.6 and Table 5.7), such as narrow peaks and high fluorescence quantum yields. In the absorption spectra, regardless of solvent polarity and alkylation pattern, a very sharp main absorption band was observed centered between 500 and 530 nm attributed to the $S_1 \leftarrow S_0$ transition. A secondary, broader and less intense band around 300-400

nm from the $S_2 \leftarrow S_0$ transition was also detected. Regarding fluorescence, emission peaks were found around 520-540 nm, resulting in rather small Stokes shifts around 300 to 600 cm^{-1} for most of these dyes. In function of solvent, absorption and emission peaks were slightly shifted by about 5-8 nm, with apolar solvents resulting in a somewhat larger red-shift than polar solvents.

Overall, absorption and emission spectra of *meso*-2,6-dichlorophenyl- and *meso*-nitrophenyl-BODIPYs were some 10 nm red-shifted when compared to the more electron-rich *meso*-mesityl and *meso*-phenyl derivatives. Relevant bathochromically shifted absorption and emission spectra for styryl **5.3p** and aryl-substituted (**5.3m**, **5.3n** and **5.7**) BODIPYs were previously reported.[1b,10] On the other hand, no significant spectral shifts were observed for the alkylated BODIPYs compared to the unsubstituted starting material **5.1**.

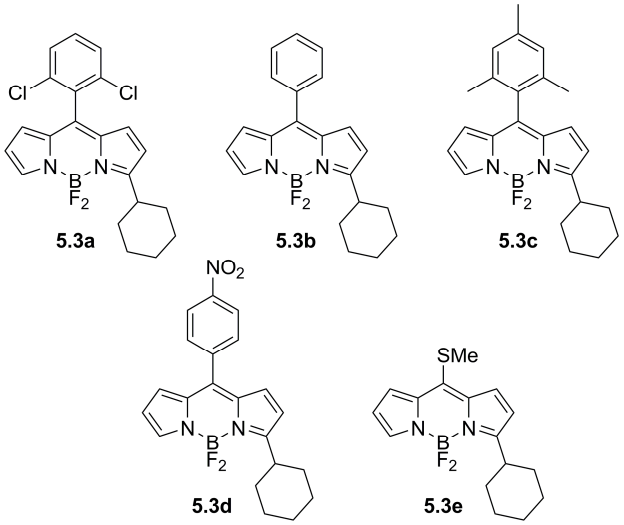


Figure 5.2: Structures of the new 3-cyclohexyl-BODIPYs **5.3a-e** for which the spectroscopic properties were measured.

Table 5.5: Spectroscopic data of 3-cyclohexyl-BODIPYs **5.3a-e** in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f[e]
5.3a	MeOH	512	524	447	887	955	0.79
	MeCN	511	525	521	908	936	0.80
	EtOAc	514	526	443	837	954	0.82
	THF	515	528	478	855	955	0.84
	Toluene	518	531	477	817	970	0.84
5.3b	MeOH	502	517	578	951	1048	0.03
	MeCN	501	516	580	989	1065	0.02
	EtOAc	503	519	613	888	956	0.04
	THF	504	520	610	976	1138	0.04
	Toluene	507	522	567	881	1077	0.08
5.3c	MeOH	502	512	389	847	868	0.99
	MeCN	502	513	427	895	856	0.99
	EtOAc	503	514	425	826	865	0.78
	THF	505	515	384	854	883	0.84
	Toluene	507	518	419	810	860	0.93
5.3d	MeOH	508	535	976	1456	1699	0.00
	MeCN	508	539	1115	1335	1557	0.00
	EtOAc	509	541	1162	1283	1447	0.01
	THF	511	535	878	1273	1322	0.01
	Toluene	515	547	1136	1177	1452	0.01
5.3e	MeOH	501	532	1163	2021	949	0.46
	MeCN	500	531	1168	1799	983	0.44
	EtOAc	502	532	1123	1888	912	0.56
	THF	504	534	1097	1873	939	0.54
	Toluene	509	538	1042	1864	957	0.60

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* fluorescein in 0.1 M NaOH(aq) ($\Phi_r = 0.90$) as a reference.

As expected, the fluorescence quantum yields were highly influenced by the substituent at the *meso*-position. Higher values were observed for *meso*-2,6-dichlorophenyl **5.3a** and *meso*-mesityl **5.3c** substituted dyes when compared to *meso*-phenyl **5.3b** and *meso*-nitrophenyl **5.3d** dyes. Free rotation of the phenyl and the nitrophenyl groups allows non-radiative decay of the excited state, resulting in low fluorescence quantum yields.[11] This rotation is sterically hindered in the 8-(2,6-

dichlorophenyl) and 8-mesityl dyes by the chlorine atoms and the methyl groups, respectively. Hence, these two chromophores are brightly fluorescent.

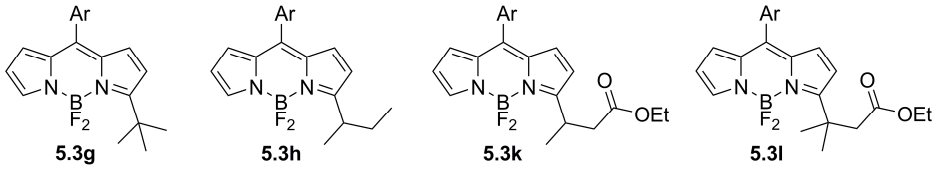


Figure 5.3: Structures of the other new 3-alkyl-BODIPYs for which the spectroscopic properties were measured (Ar = 2,6-dichlorophen-1-yl).

Table 5.6: Spectroscopic data of other 3-alkyl-BODIPYs in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f[e]
5.3g	MeOH	512	523	411	846	1025	0.92
	MeCN	511	525	522	867	1025	0.96
	EtOAc	513	526	482	817	1031	0.95
	THF	515	529	514	845	1035	0.79
	Toluene	517	530	474	810	1029	0.73
5.3h	MeOH	511	523	449	948	968	0.82
	MeCN	510	523	487	961	968	0.98
	EtOAc	512	524	447	852	983	0.94
	THF	514	527	480	902	976	0.76
	Toluene	517	528	403	882	989	0.63
5.3k	MeOH	512	524	447	854	948	0.86
	MeCN	511	524	485	899	952	0.89
	EtOAc	513	526	482	865	963	0.73
	THF	515	528	478	874	967	0.84
	Toluene	518	532	508	842	988	0.75
5.3l	MeOH	513	527	517	840	1016	0.85
	MeCN	512	525	484	912	1001	0.84
	EtOAc	514	527	480	831	1016	0.87
	THF	516	530	412	872	1014	0.67
	Toluene	518	532	508	833	1061	0.82

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* fluorescein in 0.1 M NaOH(aq) (Φ_r = 0.90) as a reference.

A particularly interesting observation is the value for the fluorescence quantum yield of the tetracyclohexylated compound **5.6b**, which was roughly 10 to 30 times higher than the one observed for the monoalkylated dye **5.3b**. For the

tetracyclohexylated fluorophore **5.6b**, the bulky cyclohexyl groups added at positions 1,7-positions of the BODIPY core hamper free rotation of the phenyl ring and consequently diminish the rate of non-radiative decay of the excited state. Hence, introduction of these bulky groups at the 1,7-positions is an interesting strategy to increase the fluorescence quantum yield of boron dipyrrins at a later stage in their synthesis. Excluding this aforementioned exception, the effect of alkylation on the quantum yield was rather limited and, in general, the usual and desired high fluorescence quantum yields were maintained.

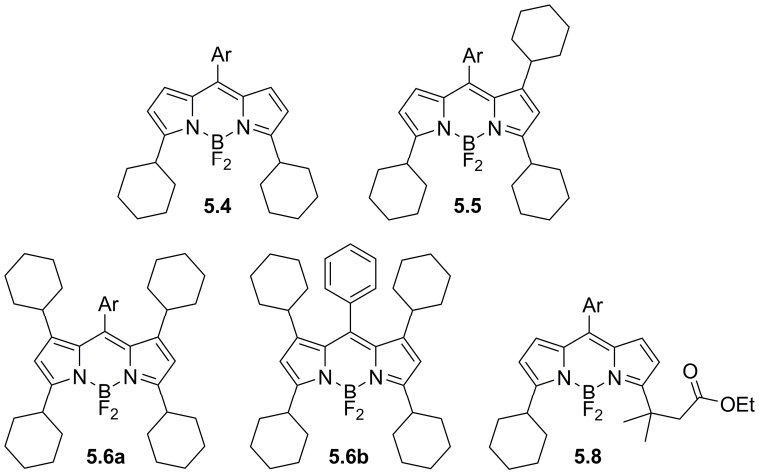


Figure 5.4: Structures of the new di-, tri- and tetraalkyl-BODIPYs **5.4**, **5.5**, **5.6** and **5.8** for which the spectroscopic properties were measured (Ar = 2,6-dichlorophen-1-yl).

Table 5.7: Spectroscopic data of di-, tri- and tetraalkyl-BODIPYs **5.4**, **5.5**, **5.6** and **5.8** in several solvents.

Dye	Solvent[a]	λ_{abs} (nm)[b]	λ_{em} (nm)[c]	$\Delta\bar{\nu}$ (cm^{-1})[d]	$fwhm_{abs}$ (cm^{-1})	$fwhm_{em}$ (cm^{-1})	Φ_f[e]
5.4	MeOH	523	533	359	689	834	0.72
	MeCN	522	534	430	672	810	0.76
	EtOAc	524	536	427	660	825	0.66
	THF	525	536	391	683	853	0.71
	Toluene	528	538	352	641	839	0.99
5.5	MeOH	520	529	327	703	840	0.75
	MeCN	519	528	328	710	830	0.85
	EtOAc	521	530	326	697	845	0.88
	THF	522	532	360	691	889	0.65
	Toluene	524	533	322	652	869	0.78
5.6a	MeOH	519	528	328	642	799	0.81
	MeCN	518	526	294	663	793	0.83
	EtOAc	518	530	437	640	800	0.88
	THF	521	529	290	663	815	0.79
	Toluene	523	531	288	618	798	0.99
5.6b	MeOH	506	513	270	691	790	0.65
	MeCN	505	512	271	694	796	0.65
	EtOAc	506	513	270	678	768	0.69
	THF	508	514	230	662	789	0.59
	Toluene	510	517	265	648	769	0.71
5.8	MeOH	521	532	397	700	1016	0.83
	MeCN	521	530	326	717	999	0.84
	EtOAc	523	533	358	702	1016	0.91
	THF	523	534	394	735	1015	0.74
	Toluene	526	536	355	698	1059	0.69

[a] Solvents are listed from top to bottom according to increasing refractive index *n*. [b] Absorption maximum. [c] Fluorescence emission maximum. [d] Stokes shift. [e] Fluorescence quantum yield determined *vs* fluorescein in 0.1 M NaOH(aq) ($\Phi_r = 0.90$) as a reference.

Fluorescence of boron dipyrrins in diluted solution is a well-known phenomenon. Solid-emissive BODIPYs, on the other hand, are far less commonly reported.[12] Nevertheless, solid emissive dyes are interesting compounds with several applications in the field of optoelectronics, such as in organic light-emitting devices[13] and solid-state dye lasers.[14] The scarcity of solid-emissive BODIPY dyes is due to the typical planarity of these fluorophores favoring intermolecular π-π interactions

resulting in nonfluorescent aggregates.[12] In this regard, the introduction of bulky substituents onto the BODIPY structure can be used to weaken the intermolecular π-stacking forces (section 4), consequently diminishing aggregation-induced fluorescence quenching and thus enabling solid state fluorescence.[12,15] Due to the bulky character of a cyclohexyl substituent, insertion of this large moiety is a feasible approach for the formation of solid-emissive BODIPYs. Hence, the emission spectra of the powders of the cyclohexylated compounds **5.3a**, **5.4**, **5.5** and **5.6a**, with respective one, two, three and four bulky alkyl groups, were studied (Figure 2). The results show that while a BODIPY dye bearing only one cyclohexyl group (**5.3a**) was virtually non-fluorescent in the solid state, introduction of extra cyclohexyl substituents onto the boron dipyrromethene core (in compounds **5.4**, **5.5** and **5.6a**) resulted in solid-state emission. The emission spectra of tricyclohexyl dye **5.5** and tetracyclohexyl dye **5.6a** reveal that solid state emission is roughly 60 nm red-shifted compared to emission in solution, while for dicyclohexyl compound **5.4** this shift is about 70 nm. The absolute quantum yields of these powders were determined to be 0.14, 0.10 and 0.11 for compounds **5.4**, **5.5** and **5.6a** respectively. The above results clearly highlight the utility of the described radical alkylation method, as it readily gives access to solid-emissive dyes by introducing multiple bulky alkyl substituents onto the BODIPY core in one reaction step. In contrast, the few solid-emissive boron dipyrrins currently described in literature require a longer synthetic route to prepare.[12]

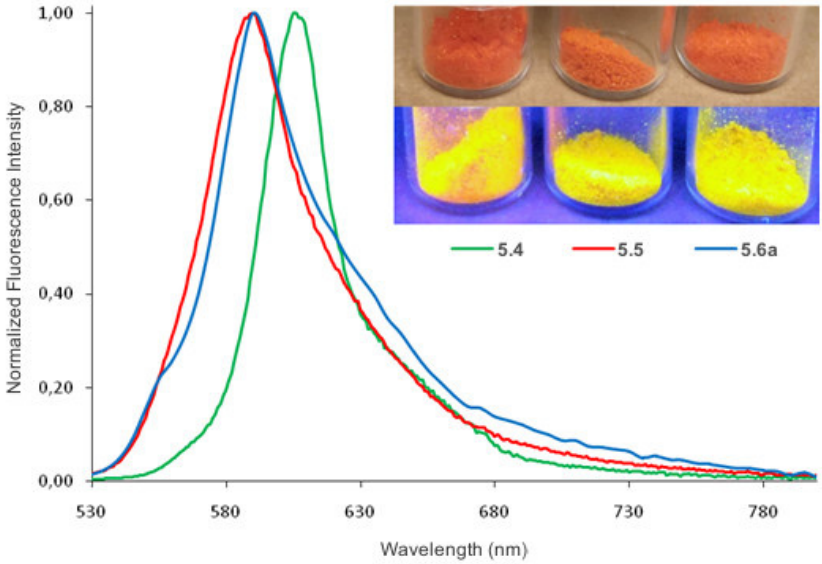


Figure 5.5: Normalized emission spectra of di-, tri- and tetracyclohexylated compounds **5.4**, **5.5** and **5.6a** in powder form. The inset shows a photograph of the powders of compounds **5.4** (left), **5.5** (middle) and **5.6a** (right) without UV irradiation (above) and with UV irradiation at 360 nm (below).

7. Conclusion

A versatile, straightforward and general method for radical C–H functionalization of BODIPY dyes, based on oxidation of boronic acids and potassium trifluoroborates with manganese(III) acetate, has been developed and investigated. This reaction proved to be a powerful tool for the alkylation of these fluorophores, allowing a broad range of alkyl groups to be introduced onto the boron dipyrromethene core. This transformation also showed limited applicability for the arylation and alkenylation of these dyes. Moreover, a similar procedure using *in situ* generated trialkylboranes was found to be a possible, though inferior, alternative. Nonetheless, this trialkylborane approach allowed the formation of a primary alkyl substituted BODIPY dye.

Furthermore, the method using potassium trifluoroborates can be modified to synthesize previously unavailable tri- and tetraalkylated BODIPY fluorophores as

well as asymmetrically alkylated derivatives. In this way, multiple bulky cycloalkyl groups can be introduced onto the core structure, which was shown to be an interesting approach to obtain solid-emissive BODIPY dyes in one reaction step. In other words, this novel radical reaction opens up new possibilities for the synthesis of new and sophisticated dyes.

8. References

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General conclusion and outlook

1. General conclusion

During this research three versatile C–H functionalization protocols for BODIPY dyes have been developed. These novel reactions allow the efficient synthesis of new, interesting and sophisticated fluorophores from simple boron dipyrrins. Furthermore, the developed methods avoid the problems of traditional functionalization strategies for boron dipyrromethenes, such as the tedious synthesis of substituted pyrrole building blocks and the manipulation of unstable intermediates. Hence, the strategies described here are powerful synthetic tools for the preparation of a broad range of BODIPY derivatives.

The first developed reaction is a palladium catalyzed C–H arylation. This transformation uses easily accessible bromoarene reagents providing a simple strategy to introduce a range of aryl substituents on the 3,5-positions. That is, as long as the bromoarene does not have strongly electron-withdrawing substituents. The optimized C–H arylation affords mono- and diarylated dyes in moderate yields. This yield is mainly restricted due to the simultaneous occurrence of mono- and diarylation. The rather forcing reaction conditions, consisting of a high reaction temperature and long reaction time, further limits the yield and scope of this transformation.

A milder arylation protocol at room temperature was developed using a ferrocene catalyzed reduction of aryldiazonium salts in the presence of a boron dipyrromethene dye. This radical C–H arylation is a fast and high yielding reaction displaying a broad scope. Using this procedure both 3-monoaryl and 3,5-diaryl dyes can be synthesized using the corresponding aryldiazonium salts. Minor downsides are that diazonium salts are not as easily accessible as bromoarenes and that some of these salts cannot be isolated. For those cases, a one-pot procedure forming *in situ* the required diazonium salts can be used instead.

Another radical transformation that was developed uses organoboranes, such as potassium trifluoroborate salts and boronic acids, as the radical precursors. Oxidation of these compounds in the presence of a BODIPY dye provides a broad range of 3-

monofunctionalized fluorophores. Radical C–H alkylation in particular is a powerful application of this procedure, introducing a great variety of alkyl substituents onto the boron dipyrrin core in good to excellent yield. However, this strategy has only a limited use in direct arylation and alkenylation. By pushing the reaction at a higher temperature di-, tri- and tetraalkylated dyes can also be prepared. Even though potassium trifluoroborate salts and boronic acids are less accessible reagents than bromoarenes, many of these compounds are nonetheless commercially available.

Several interesting reactions of limited scope were also discovered. These include oxidative transformations such as a cross-dehydrogenative C–H arylation with benzothiophene and oxidative nucleophilic substitution of hydrogen with triethylamine forming an enamine dye. Radical reactions between boron dipyrrins and radical initiators, such as benzoyl peroxide and tris(trimethylsilyl)silane, were found to be possible. Furthermore, a radical methylation in DMSO followed by a Knoevenagel type condensation provided a 3,5-distyrylated dye. Lastly, it was discovered that a BODIPY fluorophore can be oxidized to the corresponding dipyrrinone, providing a new synthetic strategy towards these compounds, including the previously unavailable 5-aryldipyrrinone. Furthermore, this 5-aryldipyrrinone could be converted into a new type of fluorophore by inserting a carbonyl bridge between the two nitrogen atoms.

The utility of these novel reactions was demonstrated by synthesizing several sophisticated compounds, including asymmetrically substituted fluorophores, annulated chromophores and solid-emissive dyes.

2. Future perspectives

The next step would be the use these powerful reactions to prepare novel BODIPY dyes for specific applications. For example, using the developed C–H arylation methods described here a possible sensor for calcium ions **0.136** can be envisaged (Figure 0.7).[1] Furthermore, these same methods could be used to introduce carbazoles moieties onto the BODIPY core. Carbazoles are common structural motifs in organic photovoltaic devices,[2] making the resulting dicarbazole dye **0.137** a possible component for these devices, either as such or after polymerization (Figure 0.7).

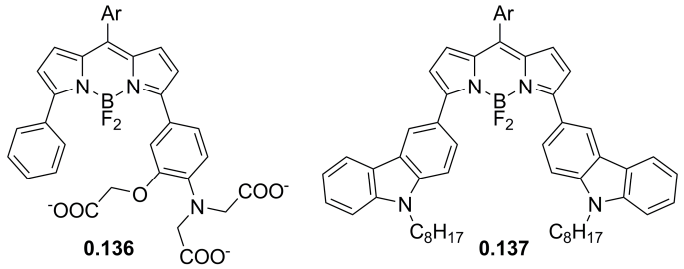


Figure 0.7: A possible calcium sensor and a possible component for organic photovoltaic devices that might be prepared using the developed C–H functionalization reaction.

Boron dipyrrin dyes are often used to label various biological molecules.[3] Using the developed C–H functionalization reactions two different labeling dyes can be designed. Utilizing either radical alkylation with a trifluoroborate (to form compound **0.138**) or radical arylation with a 4-carboxybenzenediazonium salt (to form compound **0.139**) the required acid group can be introduced and subsequently converted to an activated ester. The water solubility of both fluorophores could be improved by sulfonating with chlorosulfonic acid (Figure 0.8).

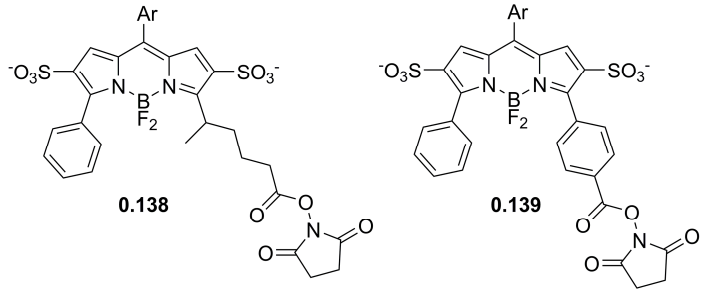
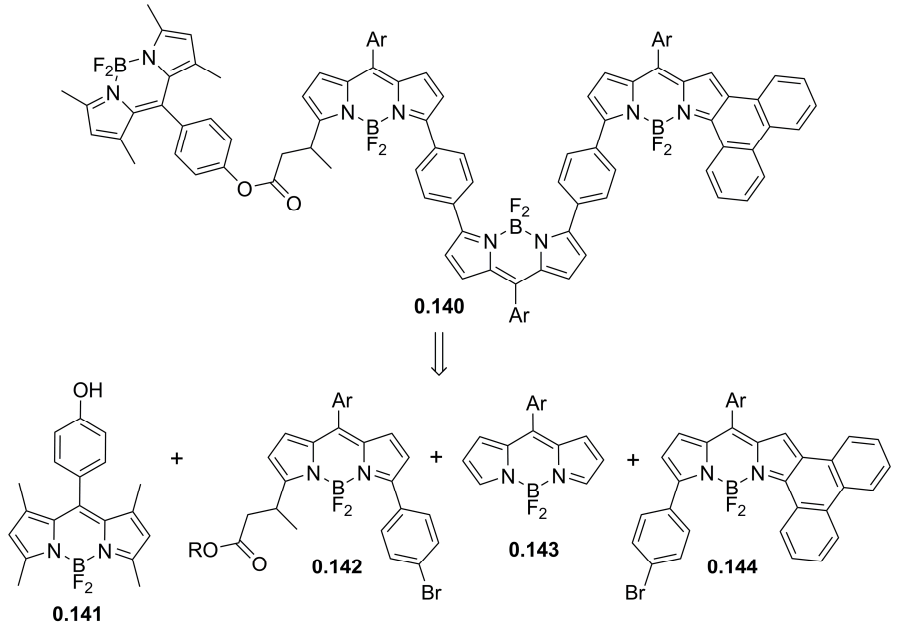


Figure 0.8: Two possible labeling reagents that might be prepared using the developed C–H functionalization reaction.

Lastly, an energy-transfer cassette[4] **0.140** consisting of four different BODIPY dyes can be conceived (Scheme 0.32). The required components might be connected using the developed palladium catalyzed C–H arylation between two bromophenyl dyes (**0.142** and **0.144**) and a 3,5-unsubstituted fluorophore **0.143** in two sequential steps. Esterification is a feasible way to attach the phenol dye **0.141** to the other three compounds. The two bromophenyl chromophores can themselves be made from the 3,5-unsubstituted compound **0.143** using the developed C–H functionalization reactions. The bromophenyl substituent can be placed on the 3-position using the

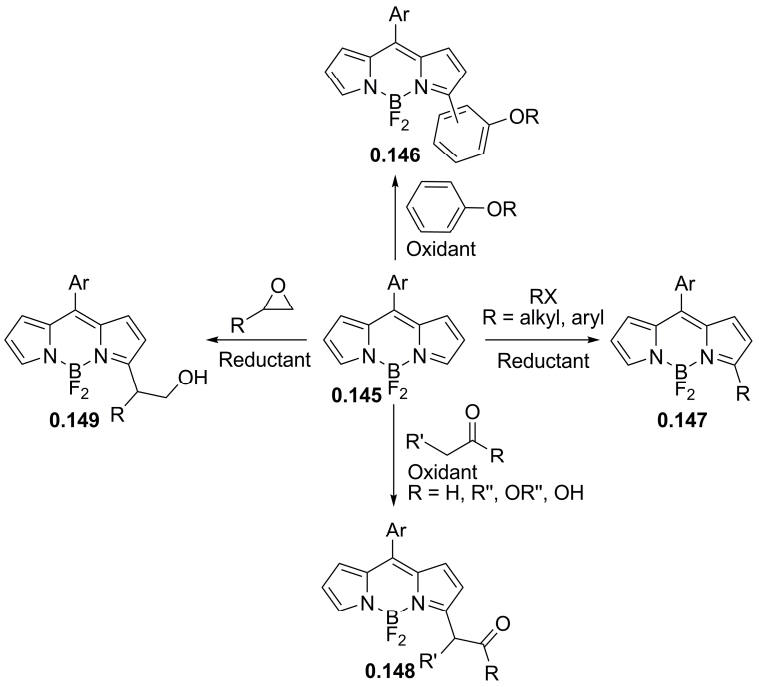
corresponding diazonium salt, and the ester functionality can be introduced with an ester trifluoroborate. The annulated side of the biphenyl-fused dye **0.144** can be made by reacting biphenyl-2-diazonium tetrafluoroborate with a 3-unsubstituted fluorophore followed by oxidative cyclization.



Scheme 0.32: Proposed synthetic strategy towards an energy-transfer cassette based on BODIPY.

The radical reactions discovered during this work are powerful methods to functionalize BODIPY dyes. However, we are currently only scratching the surface of the possibilities with these reactions and many new radical transformations for boron dipyrrins remain to be discovered. Several redox reactions generate radicals from a precursor without relying on a radical chain process and could be investigated for their potential to functionalize boron dipyrromethenes (Scheme 0.33).[5] For example, oxidation of electron rich aromatic systems, such as phenols and aromatic ethers, is known to form aryl radicals[5,6] and might give access to the corresponding aryl dyes **0.146**. Reduction of alkyl and aryl halides using a variety of metal salts also forms radicals[5] and possibly a functionalized boron dipyrrin **0.147**. Carbonyl compounds, such as aldehydes, ketones, esters and acids, can be oxidized with for example $Mn(OAc)_3 \cdot 2H_2O$ resulting in α-oxoalkyl radicals.[5,7] Reaction of these

radicals with a 3,5-unsubstituted BODIPY **0.145** would lead to a range of alkylated dyes **0.148**. A last example is a titanium(III) promoted one-electron reduction of an epoxide followed by a radical ring opening leading to a α-oxido alkyl radical[5,8] and hopefully an alkyl substituted dye **0.149**. This list of examples is far from complete and many more radical reactions to functionalize BODIPY dyes can be investigated.



Scheme 0.33: A few potential radical transformations of BODIPY dyes.

3. References

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Experimental data

Chemicals were purchased from Acros Organics, Sigma Aldrich, Alfa Aesar and TCI Europe and used as received. 8-Arylated BODIPY dyes were prepared according to published literature procedures, through a water based dipyrromethane synthesis followed by oxidation and condensation.[1] Aryldiazonium salts were synthesized *via* traditional literature procedures.[2] Lastly, non-commercial potassium trifluoroborates were synthesized using published methods.[3] All reactions were carried out in flame dried glassware, but no special precautions were taken for the exclusion of moisture. Solvents were not dried prior to use, unless stated otherwise. Most reactions were carried out under a nitrogen atmosphere.

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance 300 instrument operating at a frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C. In the case of ambiguous assignments, spectra were run on a Bruker 400 or Bruker 600 instrument. Due to the small coupling constants in pyrroles and pyrrolic dyes, the multiplicity of the signals is often unclear. In these cases, NMR signals often appear as singlets, whereas they are not. ^{1}H NMR spectra in $CDCl_3$, DMSO-d_6 and acetone-d_6 were referenced to tetramethylsilane (0.00 ppm) as an internal standard, while ^{1}H NMR spectra in THF-d_8 were referenced to the THF-d_8 signal of 1.72 ppm. ^{13}C NMR spectra in $CDCl_3$ were referenced to the $CDCl_3$ (77.16 ppm) signal, ^{13}C NMR spectra in DMSO-d_6 were referenced to the DMSO-d_6 (39.52 ppm) signal, ^{13}C NMR spectra in acetone-d_6 were referenced to the acetone-d_6 signal of 206.26 ppm and ^{13}C NMR spectra in THF-d_8 were referenced to the THF-d_8 signal of 25.31 ppm. ^{19}F NMR spectra were referenced to external $CFCl_3$ (0.00 ppm). ^{11}B NMR spectra were referenced to external $BF_3{\cdot}OEt_2$ (0.00 ppm) with a negative sign indicating an upfield shift.

Low resolution mass spectra were recorded on a Hewlett-Packard 5989A mass spectrometer (EI mode and CI mode) or a Thermo Finnigan LCQ Advantage instrument (ESI mode). High-resolution mass data on the other hand were obtained with a Kratos MS50TC instrument (EI mode), or they were acquired with a Waters Synapt G2 HDMS quadrupole orthogonal acceleration time-of-flight mass spectrometer (ESI mode), for which samples were infused at 3 µL/min and spectra

were obtained in positive or negative ionization mode with a resolution of 15000 (fwhm) using leucine enkephalin as lock mass. Melting points were taken on a Reichert Thermovar and are uncorrected.

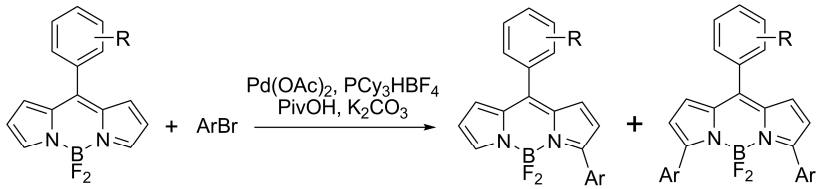
The electronic absorption spectra and absorbances were measured on a Perkin-Elmer Lambda 40 UV–vis spectrophotometer. Corrected steady-state excitation and emission spectra were recorded on a Spex Fluorolog instrument with temperature-controlled cell holder. Freshly prepared samples in 1 cm quartz cells were used to perform all UV–vis absorption and fluorescence measurements. For each dye in a specific solvent, multiple absorption and fluorescence spectra were recorded as a function of concentration. These experiments as a function of solvent allowed us to determine the spectral maxima [λ_{abs}(max) and λ_{em}(max)], the full width at half maximum of the absorption ($fwhm_{abs}$) and the fluorescence emission ($fwhm_{em}$) bands, and the Stokes shifts [$\Delta\bar{\nu} = 1/\lambda_{abs}(max) - 1/\lambda_{em}(max)$]. The standard uncertainty (square root of variance) on the absorption and emission maxima λ_{abs}(max) and λ_{em}(max) is approximately 1 nm. For the determination of the relative fluorescence quantum yields (Φ_f) in solution, only dilute solutions with an absorbance below 0.1 at the excitation wavelength were used. Measurements were performed using 10 mm optical path length cuvettes under right-angle arrangement. The average of Φ_f was calculated from multiple, independent Φ_f measurements. All spectroscopic measurements were done on non-degassed samples at 20 °C using spectroscopic grade solvents. Solid state fluorescence spectroscopy of powders was performed in an Edinburgh FLS980 fluorescence spectrometer with excitation in 485 nm and absolute fluorescence quantum yields were obtained with the same equipment using the integrating sphere accessory.

Single crystals of 2,6-di(tris(trimethylsilyl)silyl)-BODIPY **3.6**, suitable for X-ray diffraction were obtained by slow diffusion of pentane into a dichloromethane solution of the compound at room temperature over a one week period. Single crystals of 1,3,5,7-tetracyclohexyl-BODIPY **5.6a**, suitable for X-ray diffraction were obtained by slow diffusion of methanol into a dichloromethane solution of the compound at room temperature over a one week period. X-ray intensity data were collected at 100 K on an Agilent Supernova diffractometer, equipped with an Atlas

CCD detector, using Mo Kα radiation (λ = 0.71073 Å). The images were interpreted and integrated with the CrysAlisPro software from Agilent Technologies.[4] Using Olex2,[5] the structure was solved with the ShelxS[6] structure solution program using Direct Methods and refined with the ShelxL[6] refinement package using full-matrix least squares minimization on F^2. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode with isotropic temperature factors were fixed at 1.2 times U_{eq} of the parent atoms (1.5 for methyl groups).

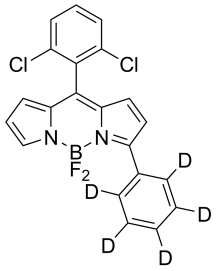
1. Synthetic procedures and characterization data from Chapter 1

General palladium catalyzed C–H arylation procedure



BODIPY **1.7** (one equivalent) was weighed together with K_2CO_3 (3 equivalents), $Pd(OAc)_2$ (5 mol%), PCy_3HBF_4 (10 mol%), pivalic acid (30 mol%) and, if a solid, the bromoarene (1.1 equivalents). This was placed in a reaction vessel with a magnetic stirring bar and dissolved in toluene (or *o*-xylene) to form a 0.1 M solution. This reaction vessel was then flushed with nitrogen. If the bromoarene (1.1 equivalents) was a liquid, it was added next using a syringe. The reaction mixture was heated to 110 °C for the indicated time. Upon completion, the reaction mixture was cooled to room temperature. Subsequently, the solution was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified chromatographically.

3-(Phenyl-d_5)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.5

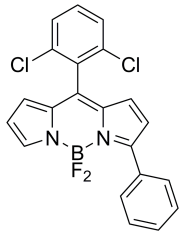


Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.4** (134.8 mg, 0.1 mmol) and bromobenzene-d_5 (11.5 µL, 0.11 mmol) in toluene for 24 h. The crude product was purified *via* column chromatography (silica; heptane/CH_2Cl_2; 2:1 v/v) providing the desired monoaryl product **1.5** (16.9 mg, 41%) and the diarylated side product **1.6** (11.0 mg, 22%).

1.5: Red-purple solid with a green luster; Mp: transition at 264 °C, melting point at 279 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (s, 1H), 7.56-7.36 (m, 3H), 6.74 (d, 1H, J = 4.2 Hz), 6.68 (d, 1H, J = 4.3 Hz), 6.62 (d, 1H, J = 3.0 Hz), 6.48 (d, 1H, J = 2.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 161.8, 145.6, 143.3, 138.8, 137.2, 135.6, 133.8, 131.8, 131.8, 131.3, 131.1, 129.5, 128.4, 128.1, 128.0, 121.8, 118.6 ppm; MS (EI, *m/z*): 417 (100%), 418 (41%), 419 (66%); HRMS (ESI-TOF, *m/z*): $[M - F]^+$ calculated for $C_{21}H_8D_5BCl_2FN_2$ 398.0847, found 398.0827.

1.6: Purple solid with a copper luster; Mp 146 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57-7.37 (m, 3H), 6.66 (d, 2H, J = 4.2 Hz), 6.61 (d, 2H, J = 4.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 137.3, 136.1, 135.9, 132.4, 132.2, 131.2, 129.2, 128.4, 128.1, 127.9, 127.6, 121.5 ppm; MS (EI, *m/z*): 498 (100%), 499 (47%), 500 (68%); HRMS (ESI-TOF, *m/z*): $[M + H]^+$ calculated for $C_{27}H_8D_{10}BCl_2F_2N_2$ 499.1536, found 499.1536; $[M - F]^+$ calculated for $C_{27}H_7D_{10}BCl_2FN_2$ 479.1474, found 479.1477.

3-Phenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9a

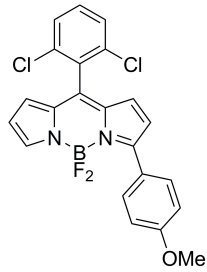


Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (134.8 mg, 0.4 mmol) and bromobenzene **1.8a** (46.5 µL, 0.44 mmol) in *o*-xylene for 24 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing the desired monoaryl product **1.9a** (73 mg, 44%) and the diarylated side product **1.10a** (34 mg, 17%).

1.9a: Red solid with a green lustre; Mp 278 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06-7.95 (m, 2H), 7.85 (s, 1H), 7.56-7.39 (m, 6H), 6.75 (d, 1H, J = 3.96 Hz), 6.68 (d, 1H, J = 3.96 Hz), 6.62 (d, 1H, J = 3.00 Hz), 6.49 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.8, 143.4, 135.6, 132.0, 131.8, 131.3, 131.1, 130.5, 129.8, 129.7, 129.6, 129.5, 128.5, 128.4, 128.1, 121.8, 118.6 ppm; MS (EI, *m/z*): 412; HRMS (EI, *m/z*): calculated for $C_{21}H_{13}BCl_2F_2N_2$ 412.05169, found 412.05171.

1.10a: Purple solid with a copper lustre; Mp 140 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96-7.86 (m, 4H), 7.54-7.37 (m, 9H), 6.66 (d, 2H, J = 4.14 Hz), 6.61 (d, 2H, J = 4.14 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.9, 135.8, 132.5, 132.2, 131.2, 129.9, 129.7, 129.7, 129.6, 129.2, 128.4, 128.3, 121.6 ppm; MS (EI, *m/z*): 488; HRMS (EI, *m/z*): calculated for $C_{27}H_{17}BCl_2F_2N_2$ 488.08299, found 488.08194.

3-*p*-Anisyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9b

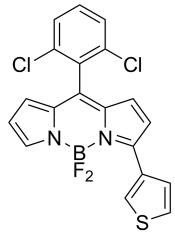


Prepared following the general procedure using 8-(2,6 dichloropheny)l-BODIPY **1.7a** (134.8 mg, 0.4 mmol) and 4-bromoanisole **1.8b** (55.0 µL, 0.44 mmol) in toluene for 43 h. The crude product was purified *via* column chromatography (silica; petroleum ether/diethyl ether; 2:1 v/v) providing the desired monoaryl product **1.9b** (74 mg, 42%) and the diarylated side product **1.10b** (21 mg, 10%).

1.9b: Dark red crystals with a copper lustre; Mp 70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 8.85 Hz), 7.80 (s, 1H), 7.52-7.37 (m, 3H), 7.02 (d, 2H, J = 8.85 Hz), 6.76-6.69 (m, 2H), 6.56 (s, 1H), 6.46 (s, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1, 161.8, 141.9, 137.5, 135.7, 132.0, 131.8, 131.7, 131.7, 131.4, 131.2, 128.3, 126.8, 124.2, 121.9, 118.0, 114.2, 55.5 ppm; MS (EI, *m/z*): 442; HRMS (EI, *m/z*): calculated for $C_{22}H_{15}BCl_2F_2N_2O$ 442.06226, found 442.06248.

1.10b: Purple crystals with a green lustre; Mp 63 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, 4H, J = 8.85 Hz), 7.52-7.38 (m, 3H), 6.97 (d, 4H, J = 8.85 Hz), 6.60 (s, 4H), 3.86 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.9, 159.1, 135.8, 132.2, 131.3, 131.3, 131.2, 130.9, 128.5, 128.2, 125.0, 120.9, 113.8, 55.3 ppm; MS (EI, *m/z*): 548; HRMS (EI, *m/z*): calculated for $C_{29}H_{21}BCl_2F_2N_2O_2$ 548.10412, found 548.10536.

3-Thien-3-yl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9e

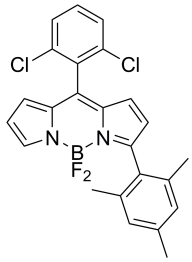


Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (33.7 mg, 0.1 mmol) and 3-bromothiophene **1.8e** (10.5 µL, 0.11 mmol) in toluene for 27 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing the desired monoaryl product **1.9e** (23 mg, 55%) and the diarylated side product **1.10e** (5 mg, 10%).

1.9e: Dark purple crystals with a green lustre; Mp 214 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (d, 1H, J = 1.53 Hz), 7.84 (s, 1H), 7.72 (d, 1H, J = 4.71 Hz), 7.53-7.35 (m, 4H), 6.80 (d, 1H, J = 4.32 Hz), 6.72 (d, 1H, J = 4.32 Hz), 6.58 (d, 1H, J = 3.39 Hz), 6.49 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.7, 142.4, 137.2, 135.6, 133.6, 132.1, 131.9, 131.3, 131.2, 130.6, 130.5, 128.9, 128.4, 127.1, 125.9, 121.8, 118.3 ppm; MS (EI, *m/z*): 418; HRMS (EI, *m/z*): calculated for $C_{19}H_{11}BCl_2F_2N_2S$ 418.00811, found 418.00869.

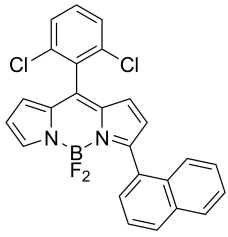
1.10e: Blue solid; Mp 205 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.37 (s, 2H), 7.69 (d, 2H, J = 4.71 Hz), 7.52-7.33 (m, 5H), 6.75 (d, 2H, J = 3.78 Hz), 6.59 (d, 2H, J = 3.78 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.2, 136.0, 135.9, 132.7, 131.1, 129.3, 129.2, 129.0, 129.0, 128.6, 128.3, 125.6, 121.1 ppm; MS (EI, *m/z*): 500; HRMS (EI, *m/z*): calculated for $C_{23}H_{13}BCl_2F_2N_2S_2$ 499.99583, found 499.99666.

3-Mesityl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9f



Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (33.7 mg, 0.1 mmol) and 2-bromo-1,3,5-trimethylbenzene **1.8f** (17.0 µL, 0.11 mmol) in toluene for 43 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 1:1 v/v) providing the desired monoaryl product **1.9f** as an orange solid with a green lustre (16 mg, 35%). Mp 152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (s, 1H), 7.55-7.39 (m, 3H), 6.96 (s, 2H), 6.79 (d, 1H, J = 4.14 Hz), 6.62 (d, 1H, J = 4.14 Hz), 6.44 (d, 1H, J = 3.75 Hz), 6.37 (d, 1H, J = 4.14 Hz), 2.34 (s, 3H), 2.17 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 143.6, 139.2, 139.1, 137.4, 135.7, 135.5, 131.8, 131.3, 131.1, 130.8, 129.1, 129.0, 128.4, 127.8, 121.7, 118.4, 21.4, 20.1 ppm; MS (EI, *m/z*): 454 (M), 434 (M - HF); HRMS (EI, *m/z*): calculated for $C_{24}H_{19}BCl_2F_2N_2$ 454.09864, found 454.09852.

3-(1-Naphthyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9g



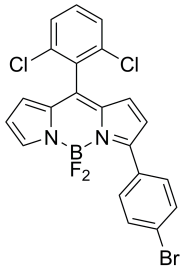
Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (134.8 mg, 0.4 mmol) and 1-bromonaphthalene **1.8g** (61.5 µL, 0.44 mmol) in *o*-xylene for 24 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing the diarylated side product **1.10g** (37 mg,

16%) and impure monoaryl compound **1.9g**. Analytically pure mononaphtyl-BODIPY **1.9g** was obtained by subsequent HPLC purification (silica; toluene/CH_2Cl_2; 2:1 v/v), providing the desired product **1.9g** (37 mg, 20%).

1.9g: Red crystals with a green lustre; Mp 282 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03-7.95 (m, 2H), 7.94-7.84 (m, 2H), 7.77 (s, 1H), 7.62 (t, 1H, J = 7.73 Hz), 7.55-7.43 (m, 5H), 6.83 (d, 1H, J = 4.14 Hz), 6.65 (m, 2H), 6.46 (d, 1H, J = 3.03 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.1, 144.0, 139.3, 136.1, 135.6, 134.2, 133.6, 131.9, 131.8, 131.3, 130.3, 130.0, 129.8, 128.6, 128.4, 126.7, 126.2, 126.1, 125.0, 123.4, 118.8 ppm; MS (EI, *m/z*): 462; HRMS (EI, *m/z*): calculated for $C_{25}H_{15}BCl_2F_2N_2$ 462.06734, found 462.06839.

1.10g: Purple solid with a copper lustre; Mp: decomposition at 310 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91-7.77 (m, 8H), 7.60-7.54 (m, 2H), 7.52-7.37 (m, 7H), 6.79 (d, 2H, J = 3.21 Hz), 6.59 (d, 2H, J = 3.39 Hz) ppm; ^{13}C NMR: product is too insoluble to obtain a fully resolved spectrum; MS (EI, *m/z*): 588; HRMS (EI, m/z): calculated for $C_{35}H_{21}BCl_2F_2N_2$ 588.11429, found 588.11553.

3-(4-Bromophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9j



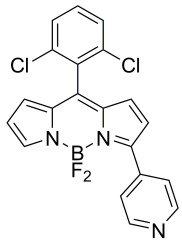
Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (134.8 mg, 0.4 mmol) and 1,4-dibromobenzene **1.8j** (61.5 µL, 0.44 mmol) in toluene for 22 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing the desired monoaryl product **1.9j** (30 mg, 15%) and the diarylated side product **1.10j** (7 mg, 3%).

1.9j: Dark crystals with a copper luster; Mp 222 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92-7.82 (m, 3H), 7.63 (d, 2H, J = 8.5 Hz), 7.53-7.35 (m, 3H), 6.73 (d, 1H, J = 4.3

Hz), 6.69-6.60 (m, 2H), 6.53-6.46 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.8, 144.2, 139.2, 137.1, 135.5, 134.1, 131.8, 131.7, 131.4, 131.2, 131.0, 130.9, 128.7, 128.4, 125.2, 121.4, 119.1 ppm; MS (EI, *m/z*): 490 (61%), 492 (100%), 494 (46%); HRMS (EI, *m/z*): calculated for $C_{21}H_{12}BBrCl_2F_2N_2$ 489.96220, found 489.96455.

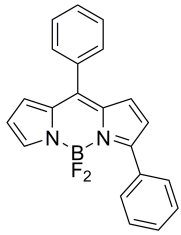
1.10j: Dark purple crystals with a green luster; Mp 324 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78 (d, 4H, J = 8.65 Hz), 7.58 (d, 4H, J = 8.65 Hz), 7.54-7.41 (m, 3H), 6.68 (d, 2H, J = 4.30 Hz), 6.60 (d, 2H, J = 3.95 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.7, 136.3, 135.7, 131.9, 131.7, 131.3, 131.2, 131.1, 131.1, 129.5, 128.4, 124.8, 121.5 ppm; MS (EI, *m/z*): 644 (38%), 646 (100%), 647 (52%), 648 (90%); HRMS (EI, *m/z*): calculated for $C_{27}H_{15}BBr_2Cl_2F_2N_2$ 643.90402, measured 643.90721.

3-(Pyridin-4-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9k



Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (33.7 mg, 0.1 mmol) and 4-bromopyridine hydrochloride **1.8k** (21.4 mg, 0.11 mmol) in toluene for 5 days. The crude product was purified *via* column chromatography (silica; CH_2Cl_2/ethyl acetate; 8:2 v/v) providing the desired monoaryl product **1.9k** as a red solid with a green luster (13 mg, 32%). Mp 230 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.75 (d, 2H, J = 5.5 Hz), 7.97 (s, 1H), 7.86 (d, 2H, J = 5.6 Hz), 7.55-7.40 (m, 3H), 6.80-6.64 (m, 3H), 6.57 (d, 1H, J = 3.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.5, 150.5, 150.1, 146.4, 140.5, 139.4, 137.0, 135.4, 135.0, 131.6, 131.4, 130.3, 128.5, 123.4, 120.8, 120.2 ppm; MS (EI, *m/z*): 413; HRMS (EI, *m/z*): calculated for $C_{20}H_{12}BCl_2F_2N_3$ 413.04694, found 413.04747.

3,8-Diphenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9l

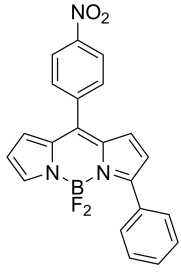


Prepared following the general procedure using 8-phenyl-BODIPY **1.7l** (53.6 mg, 0.2 mmol) and bromobenzene **1.8a** (23.0 µL, 0.22 mmol) in *o*-xylene for 28 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing the desired monoaryl product **1.9l** (21 mg, 31%) and the diarylated side product **1.10l** (27 mg, 32%).

1.9l: Red solid with a green lustre; Mp 58 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00-7.92 (m, 2H), 7.85 (s, 1H), 7.63-7.45 (m, 8H), 6.99 (d, 1H, J = 4.17 Hz), 6.86 (d, 1H, J = 3.60 Hz), 6.69 (d, 1H, J = 4.35 Hz), 6.52 (d, 1H, J = 2.46 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6, 145.8, 142.5, 137.3, 134.3, 132.9, 132.3, 130.7, 130.6, 130.1, 129.8, 129.6, 128.5, 128.5, 125.9, 121.1, 118.2 ppm; MS (EI, *m/z*): 344; HRMS (EI, *m/z*): calculated for $C_{21}H_{15}BF_2N_2$ 344.12964, found 344.13011.

1.10l: Dark purple solid; Mp 191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91-7.83 (m, 4H), 7.63-7.50 (m, 5H), 7.47-7.37 (m, 6H), 6.90 (d, 2H, J = 4.35 Hz), 6.63 (d, 2H, J = 4.17 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 144.2, 136.5, 134.4, 132.7, 131.0, 130.7, 130.2, 129.6, 128.4, 128.3, 121.0 ppm (one carbon overlap); MS (EI, *m/z*): 420; HRMS (EI, *m/z*): calculated for $C_{27}H_{19}BF_2N_2$ 420.16094, found 420.16196.

3-Phenyl-8-(*p*-nitrophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9m

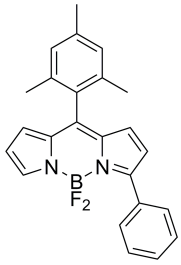


Prepared following the general procedure using 8-(*p*-nitrophenyl)-BODIPY **1.7m** (62.6 mg, 0.2 mmol) and bromobenzene **1.8a** (23.0 µL, 0.22 mmol) in *o*-xylene for 46 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 1:1 v/v) providing the desired monoaryl product **1.9m** (22 mg, 28%) and the diarylated side product **1.10m** (17 mg, 18%).

1.9m: Purple crystals with a green lustre; Mp 193 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.41 (d, 2H, J = 8.85 Hz), 8.00-7.93 (m, 2H), 7.89 (s, 1H), 7.77 (d, 2H, J = 8.67 Hz), 7.55-7.47 (m, 3H), 6.89 (d, 1H, J = 4.53 Hz), 6.79-6.70 (m, 2H), 6.55 (d, 1H, J = 3.21 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.1, 143.5, 140.4, 136.9, 133.7, 132.4, 131.8, 131.5, 130.6, 129.7, 129.6, 129.6, 129.2, 128.6, 123.8, 122.1, 118.9 ppm; MS (EI, *m/z*): 389; HRMS (EI, *m/z*): calculated for $C_{21}H_{14}BF_2N_3O_2$ 389.11471, found 389.11459.

1.10m: Dark purple solid; Mp 99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.42 (d, 2H, J = 8.67 Hz), 7.92-7.83 (m, 4H), 7.79 (d, 2H, J = 8.46 Hz), 7.49-7.39 (m, 6H), 6.79 (d, 2H, J = 4.14 Hz), 6.67 (d, 2H, J = 3.96 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.3, 140.8, 136.0, 132.3, 131.6, 130.4, 130.1, 129.7, 129.6, 129.6, 128.5, 123.7, 121.8 ppm; MS (EI, *m/z*): 465; HRMS (EI, *m/z*): calculated for $C_{27}H_{18}BF_2N_3O_2$ 465.14601, found 465.14769.

3-Phenyl-8-mesityl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.9n

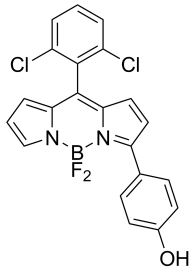


Prepared following the general procedure using 8-mesityl-BODIPY **1.7n** (38.6 mg, 0.1 mmol) and bromobenzene **1.8a** (11.5 µL, 0.11 mmol) in toluene for 48 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing the desired monoaryl product **1.9n** (8.4 mg, 22%) and the diarylated side product **1.10m** (4.8 mg, 10%).

1.9n: Orange solid with a green luster; Mp 170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03-7.92 (m, 2H), 7.81 (s, 1H), 7.55-7.43 (m, 3H), 6.97 (s, 2H), 6.73 (d, 1H, J = 4.3 Hz), 6.62 (d, 2H, J = 4.2 Hz), 6.49-6.38 (m, 1H), 2.37 (s, 3H), 2.15 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6, 145.8, 142.5, 138.9, 137.7, 136.7, 134.6, 132.3, 131.4, 130.2, 130.1, 129.6, 129.6, 128.5, 128.3, 121.1, 118.2, 21.3, 20.2 ppm; MS (EI, *m/z*): 386; HRMS (ESI-TOF, *m/z*): $[M + H]^+$ calculated for $C_{24}H_{22}BF_2N_2$ 387.1844, found 387.1841; $[M + Na]^+$ calculated for $C_{24}H_{21}BF_2N_2Na$ 409.1664, found 409.1663; $[M - F]^+$ calculated for $C_{24}H_{21}BFN_2$ 367.1782, found 367.1786.

1.10n: Purple solid with a green luster; Mp 211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92-7.85 (m, 4H), 7.47-7.38 (m, 6H), 6.99 (s, 2H), 6.66 (d, 2H, J = 4.15 Hz), 6.55 (d, 2H, J = 3.95 Hz), 2.38 (s, 3H), 2.21 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 144.1, 138.7, 137.0, 136.7, 132.8, 130.5, 129.6, 129.6, 129.5, 128.4, 128.3, 120.9, 21.3, 20.3 ppm; MS (EI, *m/z*): 462; HRMS (EI, *m/z*): calculated for $C_{30}H_{25}BF_2N_2$ 462.20789, measured 462.20927.

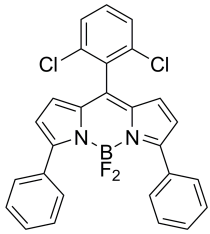
3-(4-Hydroxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.13



Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (337.0 mg, 1 mmol) and 2-(4-bromophenoxy)tetrahydro-2*H*-pyran **1.11** (282.8 mg, 1.1 mmol) in *o*-xylene. After 65 hours, the reaction mixture was cooled to room temperature. Subsequently, the solution was poured in diethyl ether (250 mL), washed three times with water (250 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. This crude reaction mixture was dissolved in MeOH (10 mL). To this solution *p*-toluenesulfonic acid monohydrate (19.0 mg, 10 mol%) was added and the reaction was stirred for one hour at room temperature. Afterwards, the reaction

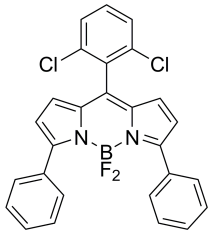
mixture was poured in diethyl ether (250 mL), washed three times with water (250 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; CH_2Cl_2/ethyl acetate; 98:2 v/v) providing a purple solid (130 mg, 30%). Mp 216 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (d, 2H, J = 8.7 Hz), 7.80 (s, 1H), 7.54-7.36 (m, 3H), 6.94 (d, 2H, J = 8.7 Hz), 6.73 (d, 1H, J = 4.5 Hz), 6.69 (d, 1H, J = 4.5 Hz), 6.57 (d, 1H, J = 3.9 Hz), 6.49-6.44 (m, 1H), 5.27 (s, br, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1, 158.1, 142.0, 137.7, 137.5, 135.7, 133.4, 132.0, 132.0, 131.5, 131.2, 128.3, 127.0, 124.4, 121.9, 118.1, 115.7 ppm; MS (EI, *m/z*): 428; HRMS (EI, *m/z*): calculated for $C_{21}H_{13}BCl_2F_2N_2O$ 428.04661, found 428.05045.

3,5-Diphenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.6



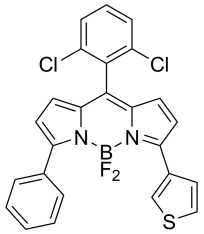
Prepared following the general procedure using 8-(2,6 dichlorophenyl)-BODIPY **1.7a** (134.8 mg, 0.4 mmol) and bromobenzene **1.8a** (92.5 µL, 0.88 mmol, 2.2 equivalents) in toluene for 4 days. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing purple crystals with a copper luster (84 mg, 43%). Characterization data is described above (compound **1.10a**).

3,5-Diphenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.6



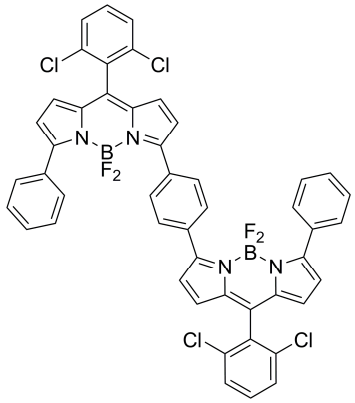
8-(2,6 dichlorophenyl)-BODIPY **1.7a** (67.4 mg, 0.2 mmol) was weighed together with K_2CO_3 (3 equivalents), $Pd(OAc)_2$ (5 mol%), PCy_3HBF_4 (10 mol%), pivalic acid (30 mol%) This was placed in a reaction vessel with a magnetic stirring bar and dissolved in toluene to form a 0.1 M solution. This reaction vessel was then flushed with nitrogen. Bromobenzene **1.8a** (5 equivalents) was added next using a syringe. The reaction mixture was heated in a microwave at 110 °C (2 min ramp time) for 3.5 hours. Upon completion, the reaction mixture was cooled to room temperature. Subsequently, the solution was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing purple crystals with a copper luster (45 mg, 46%). Characterization data is descibed above (compound **1.10a**).

3-Phenyl-5-thien-3-yl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 1.15



Prepared following the general procedure using 3-phenyl-8-(2,6-dichlorophenyl)-BODIPY **1.9a** (82.6 mg, 0.2 mmol) and 3-bromothiophene **1.8e** (20.5 µL, 0.22 mmol) in *o*-xylene for 48 h. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 3:1 v/v) providing the desired product **1.15** as a dark purple solid (61 mg, 62%). Mp 197 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32 (s, 1H), 7.97 (d, 2H, J = 6.03 Hz), 7.65 (d, 1H, J = 4.71 Hz), 7.54-7.39 (m, 6H), 7.38-7.31 (m, 1H), 6.75 (d, 1H, J = 3.93 Hz), 6.68-6.58 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 154.0, 136.2, 135.9, 132.8, 132.4, 132.2, 131.1, 129.7, 129.7, 129.4, 129.0, 128.4, 128.3, 125.6, 121.4, 121.2 ppm; MS (EI, *m/z*): 494; HRMS (EI, *m/z*): calculated for $C_{25}H_{15}BCl_2F_2N_2S$ 494.03941, found 494.04022.

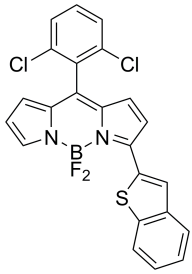
1,4-Di(3-phenyl-5-yl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene)benzene 1.16



Prepared following the general C–H arylation procedure using 3-phenyl-8-(2,6-dichlorophenyl)-BODIPY **1.9a** (148.7 mg, 0.36 mmol) and 1,4-dibromobenzene **1.8j** (35.4 mg, 0.15 mmol, 0.42 equivalents) in toluene for 53 h. The crude product was purified *via* column chromatography (silica; petroleum ether/diethyl ether; 1:1 v/v) providing the desired product **1.16** as dark crystals (31 mg, 23%). Mp: decomposition at 290 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02 (s, 4H), 7.93 (d, 4H, J = 5.85 Hz), 7.55-7.38 (m, 12 H), 6.71 (s, 2H), 6.67 (s, 4H), 6.63 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.2, 158.9, 137.1, 136.5, 136.3, 135.9, 133.4, 132.5, 132.1, 131.2, 129.9, 129.7, 129.2, 129.2, 128.4, 128.3, 121.9, 121.7 ppm (two carbons overlap); MS (ESI, *m/z*): 923 (M + Na^+), 1823 (M + M + Na^+). HRMS (ESI-TOF, *m/z*): [M - F + 2MeOH]$^+$ calculated for $C_{50}H_{36}B_2{}^{35}Cl_3{}^{37}ClF_3N_4O_2$ 945.1701, found 945.1724.

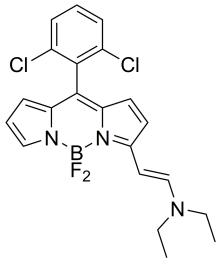
2. Synthetic procedures and characterization data from Chapter 2

3-(Benzo[*b*]thiophen-2-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 2.9



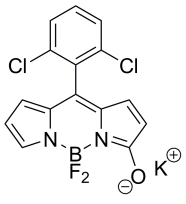
8-(2,6-Dichlorophenyl)-BODIPY **2.7** (33.7 mg, 0.1 mmol) was weighed together with K_2CO_3 (96.7 mg, 0.7 mmol, 7 equivalents), Ag_2O (162.2 mg, 0.7 mmol, 7 equivalents), 1-benzothiophene (67.1 mg, 0.5 mmol, 5 equivalents), $Pd(OAc)_2$ (1.1 mg, 5 mol%) and PCy_3HBF_4 (3.7 mg, 10 mol%) and dissolved in toluene (1 mL). The reaction vessel was flushed with nitrogen and refluxed for 24 hours. Afterwards, the reaction mixture was cooled to room temperature. Subsequently, the solution was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; heptane/CH_2Cl_2; 6:4 v/v) providing a dark purple solid with a copper luster (7.7 mg, 16%). Mp 209 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (s, 1H), 8.01-7.88 (m, 2H), 7.87-7.79 (m, 1H), 7.54-7.35 (m, 5H), 6.90 (d, 1H, J = 4.4 Hz), 6.71 (d, 1H, J = 4.4 Hz), 6.63 (d, 1H, J = 3.7 Hz), 6.53 (d, 1H, J = 2.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 143.8, 143.0, 141.4, 140.8, 137.8, 135.6, 134.3, 132.9, 131.7, 131.3, 130.8, 129.4, 128.4, 128.1, 126.5, 125.7, 125.1, 122.3, 122.1, 119.1 ppm; MS (EI, *m/z*): 468 (100%), 469 (46%), 470 (73%); HRMS (ESI-TOF, *m/z*): $[M + H]^+$ calculated for $C_{23}H_{14}BCl_2F_2N_2S$ 469.0316, found 469.0310; $[M - F]^+$ calculated for $C_{23}H_{13}BCl_2FN_2S$ 449.0254, found 449.0253.

3-(2-(Diethylamino)vinyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 2.14



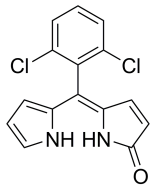
8-(2,6-Dichlorophenyl)-BODIPY **2.7** (33.7 mg, 0.1 mmol) and Ag_2O (69.5 mg, 0.3 mmol, 3 equivalents) were dissolved in DMSO (1 mL). To this mixture triethylamine (42.0 µL, 0.3 mmol, 3 equivalents) was added and this was heated at 110 °C for 5 hours. Afterwards, the reaction mixture was cooled to room temperature. Then the reaction was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; heptane/ethyl acetate; 1:1 v/v) providing a purple solid with a copper luster (27.5 mg, 63%). Mp 125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47-7.28 (m, 5H), 6.64 (d, 1H, J = 4.9 Hz), 6.55 (d, 1H, J = 4.9 Hz), 6.33-6.25 (m, 1H), 6.15-6.05 (m, 2H), 3.42 (s, br, 4H), 1.30 (t, 6H, J = 7.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.7, 150.3, 137.8, 136.5, 133.2, 131.8, 131.3, 130.3, 128.1, 125.4, 118.8, 117.5, 113.5, 91.2, 43.2, 12.1 ppm (one carbon overlap); MS (EI, *m/z*): 433 (100%), 434 (39%), 435 (67%); HRMS (ESI-TOF, *m/z*): $[M + H]^+$ calculated for $C_{21}H_{21}BCl_2F_2N_3$ 434.1174, found 434.1156; $[M - F]^+$ calculated for $C_{21}H_{20}BCl_2FN_3$ 414.1111, found 414.1097.

3-Oxido-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 2.15



8-(2,6-Dichlorophenyl)-BODIPY **2.7** (33.7 mg, 0.1 mmol), K_2CO_3 (20.7 mg, 0.15 mmol, 1.5 equivalents) and $Cu(OAc)_2$ (1.8 mg, 10 mol%) were dissolved in DMSO-d_6 (1 mL). This reaction mixture was stirred at 110 °C in the presence of air for 1 hour. Afterwards, the solution was filtered and the filtrate was used for further analysis. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.62-7.53 (m, 2H), 7.53-7.42 (m, 1H), 6.92 (s, 1H), 6.53 (dd, 1H, J_1 = 5.2 Hz, J_2 = 1.5 Hz), 6.04-5.94 (m, 1H), 5.87 (dd, 1H, J_1 = 5.2 Hz, J_2 = 1.6 Hz), 5.46 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 173.9, 136.0, 134.8, 133.3, 133.2, 131.0, 130.5, 128.2, 123.9, 123.3, 111.7, 109.8, 107.5, 79.2, 40.4, 40.1, 39.8, 39.5, 39.2, 39.0, 38.7 ppm; MS (ESI, *m/z*): 351 (M^-), 743 (M^- + M^- + K^+).

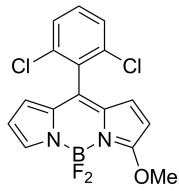
5-(2,6-Dichlorophen-1-yl)-dipyrrin-1-one 2.18



8-(2,6-Dichlorophenyl)-BODIPY **2.7** (168.5 mg, 0.5 mmol), K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equivalents) and $Cu(OAc)_2$ (9.1 mg, 10 mol%) were dissolved in DMSO (5 mL). This reaction mixture was stirred at 110 °C in the presence of air for 1 hour. Afterwards, the reaction was cooled to room temperature and flushed with nitrogen. To this aqueous HCl (37%) (0.2 mL, 2.5 mmol, 5 equivalents) was added. The reaction vessel was wrapped in aluminium foil and the reaction was stirred at room temperature for 16 hours. Upon completion, the reaction mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; heptane/ethyl acetate; 1:1 v/v) with aluminium foil wrapped around the column providing a yellow solid (135.4 mg, 89%). Mp: transition at 186 °C, melting point at 205 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.73 (s, br, 1H), 9.48 (s, br, 1H), 7.52-7.40 (m, 2H), 7.40-7.30 (m, 1H), 7.04 (s, 1H), 6.59 (d, 1H, J = 5.3 Hz), 6.30 (s, 1H), 6.18 (s, 1H), 6.13 (d, 1H, J = 5.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.6, 137.5, 137.1, 134.8, 132.1, 130.5, 128.4, 127.5, 123.5, 122.3, 114.7, 111.1,

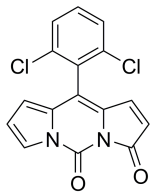
108.8 ppm; MS (EI, *m/z*): 304 (100%), 305 (24%), 306 (67%); HRMS (ESI-TOF, *m/z*): $[M + H]^+$ calculated for $C_{15}H_{11}Cl_2N_2O$ 305.0248, found 305.0245.

3-Methoxy-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 2.19



8-(2,6-Dichlorophenyl)-BODIPY **2.7** (33.7 mg, 0.1 mmol), K_2CO_3 (20.7 mg, 0.15 mmol, 1.5 equivalents) and $Cu(OAc)_2$ (1.8 mg, 10 mol%) were dissolved in DMSO (1 mL). This reaction mixture was stirred at 110 °C in the presence of air for 1 hour. Afterwards, the reaction was cooled to room temperature and flushed with nitrogen. To this Me_2SO_4 (95.0 µL, 1 mmol, 10 equivalents) was added and the reaction was stirred at room temperature for 26 hours. Upon completion, the reaction mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; heptane/CH_2Cl_2; 1:2 v/v) providing an orange solid with a green luster (3.6 mg, 10%). Mp 89 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H), 7.49-7.42 (m, 2H), 7.42-7.35 (m, 1H), 6.76 (d, 1H, J = 4.8 Hz), 6.48-6.30 (m, 2H), 6.14 (d, 1H, J = 4.8 Hz), 4.17 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 138.7, 135.9, 134.0, 131.5, 131.1, 129.8, 128.3, 128.0, 126.8, 124.4, 116.4, 105.1, 59.5 ppm; MS (EI, *m/z*): 366 (M), 351(M - CH_3); HRMS (ESI-TOF, m/z): $[M + H]^+$ calculated for $C_{16}H_{12}BCl_2F_2N_2O$ 367.0388, found 367.0379; $[M - F]^+$ calculated for $C_{16}H_{11}BCl_2FN_2O$ 347.0326, found 347.0316.

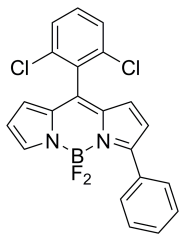
***N*,*N*'-Carbonyl-5-(2,6-dichlorophen-1-yl)-dipyrrin-1-one 2.26**



5-(2,6-Dichlorophen-1-yl)-dipyrrin-1-one **2.18** (30.5 mg, 0.1 mmol), CDI (81.1 mg, 0.5 mmol, 5 equivalents) were dissolved in dry DCM (7 mL). To this was added 4 Å molecular sieves (100 mg) and DBU (75.0 µL, 0.5 mmol, 5 equivalents), and the mixture was refluxed for 15 minutes. Afterwards, the solution was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; CH_2Cl_2/ethyl acetate; 98:2 v/v) providing a yellow solid (26.6 mg, 80%). Mp: transition at 176 °C, melting point at 201-203 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88-7.83 (m, 1H), 7.54-7.47 (m, 2H), 7.46-7.38 (m, 1H), 6.97 (d, 1H, J = 5.9 Hz), 6.57-6.50 (m, 1H), 6.22 (d, 1H, J = 5.9 Hz), 6.18-6.13 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 141.6, 136.5, 136.2, 131.5, 130.9, 129.5, 129.1, 128.7, 123.2, 121.7, 116.0, 112.8, 112.6 ppm; MS (EI, *m/z*): 330 (100%), 331 (20%), 332 (67%); HRMS (ESI-TOF, m/z): $[M + H]^+$ calculated for $C_{16}H_9Cl_2N_2O_2$ 331.0041, found 331.0035.

3. Synthetic procedures and characterization data from Chapter 3

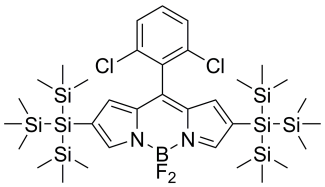
3-Phenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 3.4



8-(2,6-Dichlorophenyl)-BODIPY **3.1** (33.7 mg, 0.1 mmol) and benzoyl peroxide (24.2 mg, 0.1 mmol, 1 equivalent) were dissolved in toluene (1 mL). This reaction mixture was refluxed for 3 days. After 24 and 48 hours extra benzoyl peroxide (24.2 mg, 0.1 mmol, 1 equivalent) was added. Afterwards, the reaction was cooled to room temperature, poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; heptane/CH_2Cl_2; 6:4 v/v) providing a red

solid with a green lustre (10 mg, 24%). Characterization data is described in the part about Chapter 1 (compound **1.9a**).

2,6-Di(tris(trimethylsilyl)silyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 3.6

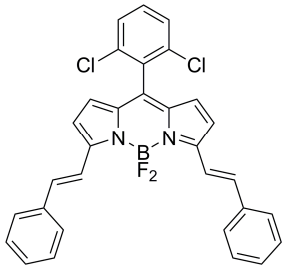


8-(2,6-Dichlorophenyl)-BODIPY **3.1** (33.7 mg, 0.1 mmol) was dissolved in acetone (1 mL) and refluxed for 68 hours. A solution in acetone (0.5 mL) containing $(TMS)_3SiH$ (61.5 µL, 0.2 mmol, 2 equivalents), AIBN (32.8 mg, 0.2 mmol, 2 equivalents) and bromobenzene (10.5 µL, 0.1 mmol, 1 equivalent) was added dropwise to the reaction mixture over a period of 8 hours. After 68 hours, the reaction was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; heptane/CH_2Cl_2; 1:1 v/v) providing a disilylated product **3.6** (45 mg, 54%) and a monosilylated product **3.5** (23 mg, 39%).

3.6: Dark purple solid; Mp 226 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (s, 2H), 7.54-7.37 (m, 3H), 6.58 (s, 2H), 0.16 (s, 54H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.8, 137.9, 136.7, 136.3, 135.4, 131.6, 131.3, 128.2, 123.6, 1.1 ppm; MS (EI, *m/z*): 635 (M - $2Me_3SiF$ - B + $2H^+$).

3.5: Red-purple solid; Mp: product is not crystalline; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 (s, 1H), 7.86 (s, 1H), 7.53-7.38 (m, 3H), 6.65 (d, 1H, J = 4.0 Hz), 6.62 (s, 1H), 6.48 (d, 1H, J = 3.1 Hz), 0.17 (s, 27H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.1, 144.1, 138.6, 138.5, 136.8, 135.3, 134.4, 131.5, 131.3, 129.4, 128.3, 124.5, 118.7, 1.1 ppm; MS (EI, *m/z*): 582 (M), 490 (M - Me_3SiF), 389 (M - $2Me_3SiF$ - B + $2H^+$); HRMS (EI, *m/z*): calculated for $C_{24}H_{35}BCl_2F_2N_2Si_4$ 582.13155, found 582.13095.

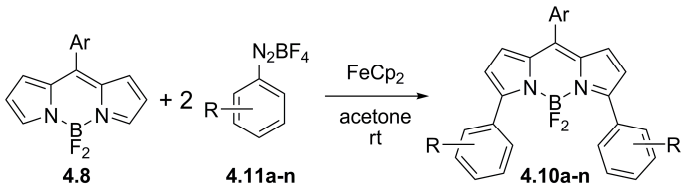
3,5-Distyryl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 3.17



8-(2,6-Dichlorophenyl)-BODIPY **3.1** (33.7 mg, 0.1 mmol) was dissolved in DMSO (0.9 mL). To this solution was added hydrogen peroxide (19.0 µL of a 35% solution in water, 0.22 mmol, 2.2 equivalents) and a $FeSO_4 \cdot 7H_2O$ solution (0.1 ml of a 0.001 M solution in DMSO, 0.1 mol%). This reaction was stirred at room temperature for one hour. Afterwards, the solution was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was dissolved in toluene (1 mL) and to this solution were added benzaldehyde (40.5 µL, 0.4 mmol, 4 equivalents), piperidine (0.05 mL), acetic acid (0.05 mL) and 4 Å molecular sieves (100 mg). The reaction vessel was then flushed with nitrogen and the reaction mixture was heated in a microwave at 110 °C (200 W) for 45 minutes. Upon completion, the reaction mixture was cooled to room temperature, poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified *via* column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing a blue solid with a green metallic luster (25.0 mg, 46%). Mp: transition at 262 °C, melting point at 328 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, 2H, J = 16.2 Hz), 7.66 (d, 4H, J = 7.4 Hz), 7.50-7.32 (m, 11H), 6.92 (d, 2H, J = 4.2 Hz), 6.57 (d, 2H, J = 4.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 137.6, 136.6, 136.1, 136.0, 132.7, 132.1, 131.0, 129.4, 129.0, 128.3, 128.1, 127.9, 119.5, 117.1 ppm; MS (EI, *m/z*): 540 (100%), 541 (47%), 542 (68%); HRMS (EI, *m/z*): calculated for $C_{31}H_{21}BCl_2F_2N_2$ 540.11429, found 540,11484.

4. Synthetic procedures and characterization data from Chapter 4

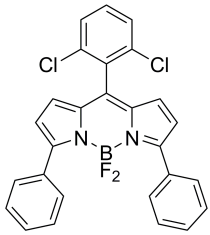
General radical C–H diarylation procedure



4.8 **4.11a-n** **4.10a-n**

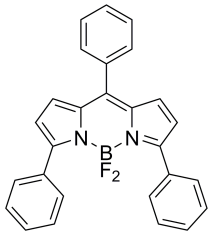
BODIPY **4.8** (0.1 mmol) and aryldiazonium tetrafluoroborate salt **4.11a-n** (0.25 mmol) were dissolved in acetone (0.8 mL). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (9.3 mg, 0.05 mmol in 0.2 mL acetone) over 15 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified chromatographically.

3,5-Diphenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10a



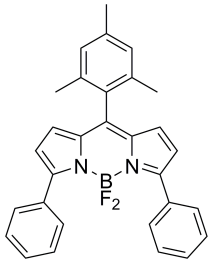
Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and benzenediazonium tetrafluoroborate **4.11a** (48.0 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing a purple solid with a copper luster (41.0 mg, 84%). Characterization data is described in the part about Chapter 1 (compound **1.10a**).

3,5,8-Triphenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10b



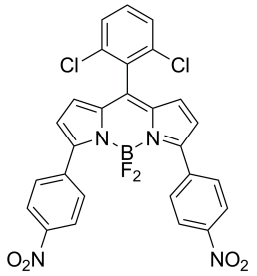
Prepared according to the general procedure for radical C–H diarylation using 8-phenyl-BODIPY **4.8b** (26.8 mg, 0.1 mmol) and benzenediazonium tetrafluoroborate **4.11a** (48.0 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v followed by silica; petroleum ether/ethyl acetate; 9:1 v/v) providing a dark purple solid (25.3 mg, 60%). Characterization data is described in the part about Chapter 1 (compound **1.10l**).

3,5-Diphenyl-8-mesityl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10c



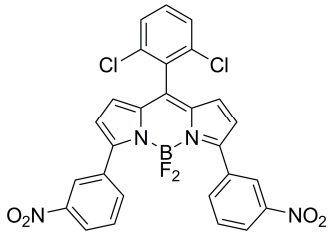
Prepared according to the general procedure for radical C–H diarylation using 8-mesityl-BODIPY **4.8c** (31.0 mg, 0.1 mmol) and benzenediazonium tetrafluoroborate **4.11a** (48.0 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing a purple solid with a green luster (29.8 mg, 65%). Characterization data is described in the part about Chapter 1 (compound **1.10n**).

3,5-Di(4-nitrophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10d



Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-nitrobenzenediazonium tetrafluoroborate **4.11d** (47.4 mg, 0.2 mmol). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (7.4 mg, 0.04 mmol in 0.2 mL acetone) over 12 minutes. The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 1:1 v/v followed by silica; petroleum ether/CH_2Cl_2; 4:6 v/v) providing a purple solid with a green metallic luster (44.4 mg, 77%). Mp 330 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.31 (d, 4H, J = 8.85 Hz), 8.06 (d, 4H, J = 8.85 Hz), 7.59-7.45 (m, 3H), 6.79 (d, 2H, J = 4.30 Hz), 6.71 (d, 2H, J = 4.30 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.6, 148.4, 138.1, 137.0, 135.5, 131.7, 131.3, 130.5, 130.5, 128.5, 123.7, 122.6, 122.2 ppm; MS (EI, *m/z*): 578 (100%), 579 (49%), 580 (69%); HRMS (EI, *m/z*): calculated for $C_{27}H_{15}BCl_2F_2N_4O_4$ 578.05315, measured 578.05528.

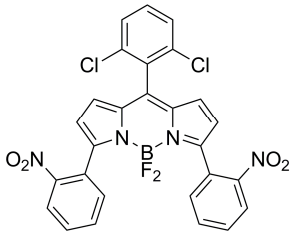
3,5-Di(3-nitrophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10e



Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 3-nitrobenzenediazonium

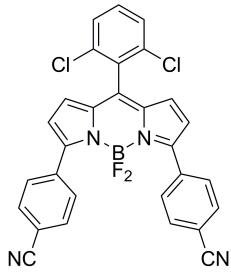
tetrafluoroborate **4.11e** (59.3 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 6:4 v/v followed by silica; petroleum ether/CH_2Cl_2; 4:6 v/v) providing a red solid (39.3 mg, 51%). Mp 148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.69 (t, 2H J = 1.90 Hz), 8.37-8.24 (m, 4H), 7.65 (t, 2H, J = 8.00 Hz), 7.58-7.44 (m, 3H), 6.79 (d, 2H, J = 4.15 Hz), 6.72 (d, 2H, J = 4.15 Hz) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.4, 148.3, 136.7, 135.6, 135.5, 135.5, 135.5, 133.7, 131.7, 131.4, 130.4, 129.6, 128.5, 124.6, 121.8 ppm; MS (EI, *m/z*): 578; HRMS (ESI-TOF, *m/z*): $[M + K]^+$ calculated for $C_{27}H_{15}BCl_2F_2KN_4O_4$ 617.0169, measured 617.0166.

3,5-Di(2-nitrophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10f



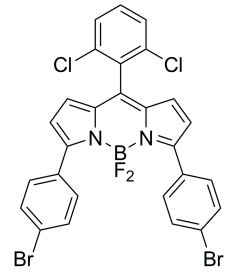
Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 2-nitrobenzenediazonium tetrafluoroborate **4.11f** (47.4 mg, 0.2 mmol). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (7.4 mg, 0.04 mmol in 0.2 mL acetone) over 12 minutes. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 1:2 v/v) providing a red solid with a copper luster (41.9 mg, 72%). Mp: decomposition at 320 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (d, 2H, J = 7.90 Hz), 7.66-7.60 (m, 3H), 7.57-7.50 (m, 4H), 7.45 (t, 2H, J = 8.05 Hz), 6.74 (d, 2H, J = 4.10 Hz), 6.41 (d, 2H, J = 4.15 Hz) ppm; ^{13}C NMR: product is too insoluble to obtain a fully resolved spectrum; MS: product cannot be ionized; HRMS: product cannot be ionized.

3,5-Di(4-cyanophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10g



Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-cyanobenzenediazonium tetrafluoroborate **4.11g** (54.3 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 1:2 v/v) providing a dark purple solid with a green metallic luster (46.3 mg, 86%). Mp: transition at 315 °C, melting point at 345 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, 4H, J = 8.65 Hz), 7.74 (d, 4H, J = 8.65 Hz), 7.57-7.44 (m, 3H), 6.77 (d, 2H, J = 4.15 Hz), 6.67 (d, 2H, J = 4.30 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.9, 136.9, 136.3, 135.6, 132.2, 131.7, 131.4, 130.3, 130.2, 130.1, 128.5, 122.0, 118.6, 113.4 ppm; MS (EI, *m/z*): 538; HRMS (EI, *m/z*): calculated for $C_{29}H_{15}BCl_2F_2N_4$ 538.07349, measured 538.07361.

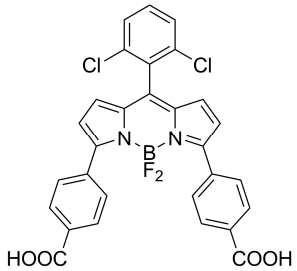
3,5-Di(4-bromophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10h



Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-bromobenzenediazonium tetrafluoroborate **4.11h** (54.0 mg, 0.2 mmol). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (7.4 mg, 0.04 mmol in 0.2 mL

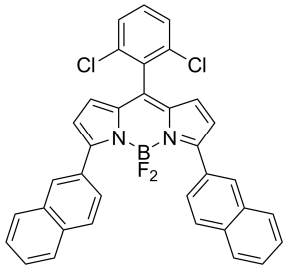
acetone) over 12 minutes. The crude product was purified by column chromatography (silica; petroleum ether/toluene; 2:1 v/v followed by silica; petroleum ether/diethyl ether; 4:1 v/v) providing dark purple crystals with a green luster (34.5 mg, 53%). Characterization data is described in the part about Chapter 1 (compound **1.10j**).

3,5-Di(4-carboxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10i



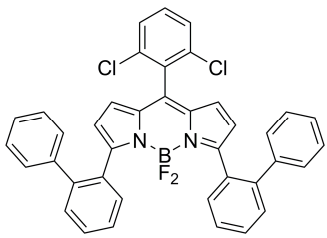
Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-carboxybenzenediazonium tetrafluoroborate **4.11i** (59.0 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; CH_2Cl_2/methanol/acetic acid; 94:6:0.1 v/v/v) providing a purple solid (40.0 mg, 69%). Mp > 350 °C; ^{1}H NMR (THF-d_8, 300 MHz): δ 8.06 (s, 8H), 7.67-7.53 (m, 3H), 6.84 (d, 2H, J = 4.30 Hz), 6.80 (d, 2H, J = 4.35 Hz) ppm; ^{13}C NMR (THF-d_8, 150 MHz): δ 167.2, 159.8, 137.5, 137.0, 136.3, 132.7, 132.6, 130.4, 130.4, 130.4, 130.3, 130.2, 129.3, 122.7 ppm; MS (EI, *m/z*): 576; HRMS (EI, *m/z*): calculated for $C_{29}H_{17}BCl_2F_2N_2O_4$ 576.06265, measured 576.06637.

3,5-Di(2-naphthyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10j



Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and naphthalene-2-diazonium tetrafluoroborate **4.11j** (60.5 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v, followed by silica; petroleum ether/toluene; 1:1 v/v) providing a dark purple solid with a green metallic luster (31.8 mg, 54%). Mp 311 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.43 (s, 2H), 8.05 (dd, 2H, J_1 = 8.65 Hz, J_2 = 1.70 Hz), 7.94-7.79 (m, 6H), 7.57-7.41 (m, 7H), 6.79-6.68 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 136.4, 136.0, 133.9, 133.1, 132.3, 131.2, 130.0, 130.0, 130.0, 129.2, 129.1, 128.4, 128.0, 127.8, 127.3, 126.8, 126.4, 122.0 ppm; MS (EI, *m/z*): 588; HRMS (EI, *m/z*): calculated for $C_{35}H_{21}BCl_2F_2N_2$ 588.11429, measured 588.11289.

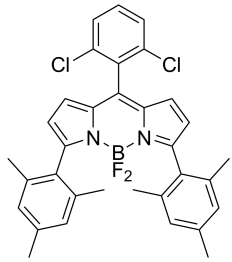
3,5-Bis(biphenyl-2-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10k



Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (134.8 mg, 0.4 mmol) and biphenyl-2-diazonium tetrafluoroborate **4.11k** (268.0 mg, 1.0 mmol) in acetone (3.2 mL). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (37.2 mg, 0.2

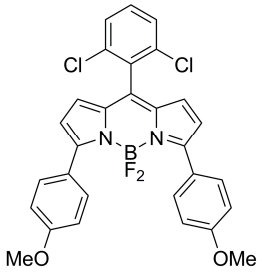
mmol in 0.8 mL acetone) over 1 hour. The crude product was purified by column chromatography (silica; heptane/CH_2Cl_2; 6:4 v/v) providing a red-purple solid (129.2 mg, 50%). Mp 348 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.92 (d, 2H, J = 7.6 Hz), 7.49-7.40 (m, 8H), 7.38-7.32 (m, 5H), 7.25-7.21 (m, 6H), 6.32 (d, 2H, J = 4.1 Hz), 5.76 (d, 2H, J = 4.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.9, 142.0, 141.5, 136.9, 135.6, 134.8, 132.2, 131.7, 131.2, 131.0, 129.7, 129.6, 129.6, 128.2, 128.0, 127.8, 127.2, 127.0, 123.3 ppm; MS (EI, *m/z*): 640 (M), 620 (M - HF); HRMS (ESI-TOF, *m/z*): $[M - F]^+$ calculated for $C_{39}H_{25}BCl_2FN_2$ 621.1472, found 621.1479.

3,5-Dimesityl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10l



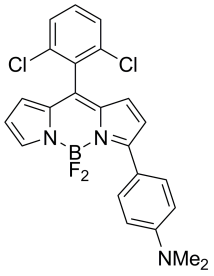
Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 2,4,6-trimethylbenzenediazonium tetrafluoroborate **4.11l** (58.5 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 7:3 v/v) providing an orange solid with a green luster (11.0 mg, 19%). Mp: decomposition at 320 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56-7.40 (m, 3H), 6.83 (s, 4H), 6.69 (d, 2H, J = 4.15 Hz), 6.24 (d, 2H, J = 3.95 Hz), 2.25 (s, 6H), 2.11 (s, 12H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.1, 138.5, 137.8, 137.4, 135.7, 134.9, 132.2, 131.1, 129.9, 129.0, 128.3, 127.7, 121.0, 21.3, 20.3 ppm; MS (EI, *m/z*): 572 (M), 552 (M - HF); HRMS (EI, *m/z*): calculated for $C_{33}H_{29}BCl_2F_2N_2$ 572.17689, measured 572.17554.

3,5-Di(4-methoxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10m



Prepared according to the general procedure for radical C–H diarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-methoxybenzenediazonium tetrafluoroborate **4.11m** (55.5 mg, 0.25 mmol). The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 2:1 v/v followed by silica; petroleum ether/CH_2Cl_2; 1:1 v/v) providing a purple solid with a green luster (16.2 mg, 30%). Characterization data is described in the part about Chapter 1 (compound **1.10b**).

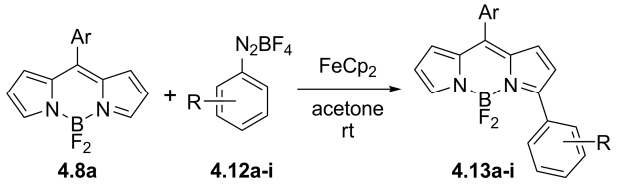
3-(4-(Dimethylamino)phenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13i



8-(2,6-Dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-(dimethylamino)benzenediazonium tetrafluoroborate **4.11n** (58.8 mg, 0.25 mmol) were dissolved in acetone (0.9 mL). To this reaction mixture was added dropwise, at room temperature, a decamethylferrocene solution (16.3 mg, 0.05 mmol in 0.2 mL CH_2Cl_2) over 15 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three

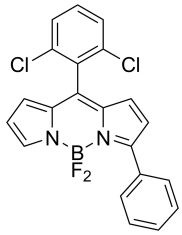
times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether/triethylamine; 66:34:0.1 v/v/v followed by silica; petroleum ether/CH_2Cl_2/triethylamine; 40:60:0.1 v/v/v) providing a green solid with a metallic luster (15.9 mg, 35%). Mp 200 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (d, 2H, J = 9.25 Hz), 7.71 (s, 1H), 7.51-7.35 (m, 3H), 6.84-6.74 (m, 3H), 6.70 (d, 1H, J = 4.70 Hz), 6.46-6.38 (m, 2H), 3.10 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.2, 138.8, 135.9, 132.6, 132.4, 132.2, 132.2, 132.1, 131.5, 130.9, 128.3, 124.1, 122.4, 118.5, 116.6, 111.6, 103.6, 40.2 ppm; MS (EI, *m/z*): 455 (100%), 456 (45%), 457 (68%); HRMS (EI, *m/z*): calculated for $C_{23}H_{18}BCl_2F_2N_3$ 455.09389, measured 455.0947.

General radical C–H monoarylation procedure



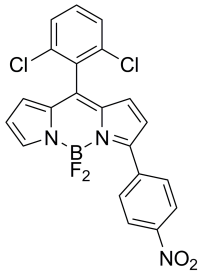
BODIPY **4.8a** (0.1 mmol) and aryldiazonium tetrafluoroborate salt **4.12a-i** (0.1 mmol) were dissolved in acetone (0.8 mL). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (3.7 mg, 0.02 mmol in 0.2 mL acetone) over 6 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified chromatographically.

3-Phenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13a



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and benzenediazonium tetrafluoroborate **4.12a** (19.2 mg, 0.1 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing a red solid with a green luster (23.9 mg, 58%). Characterization data is described in the part about Chapter 1 (compound **1.9a**).

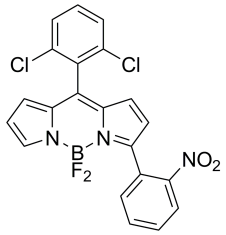
3-(4-Nitrophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13b



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-nitrobenzenediazonium tetrafluoroborate **4.12b** (23.7 mg, 0.1 mmol). The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 2:1 v/v followed by silica; petroleum ether/CH_2Cl_2; 4:6 v/v) providing a purple solid with a copper luster (22.7 mg, 50%). Mp 236 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.34 (d, 2H, J = 8.85 Hz), 8.14 (d, 2H, J = 8.85 Hz), 7.96 (s, 1H), 7.56-7.41 (m, 3H), 6.78-6.72 (m, 2H), 6.69 (d, 1H, J = 4.15 Hz), 6.57 (d, 1H, J = 3.95 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 148.3, 146.4, 140.4, 138.3, 137.1, 135.4, 135.0,

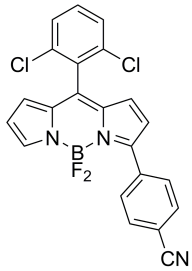
131.6, 131.4, 130.5, 130.5, 130.4, 128.5, 123.7, 121.1, 120.3 ppm; MS (EI, *m/z*): 457 (100%), 458 (43%), 459 (69%); HRMS (EI, *m/z*): calculated for $C_{21}H_{12}BCl_2F_2N_3O_2$ 457.03677, measured 457.03817.

3-(2-Nitrophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13c



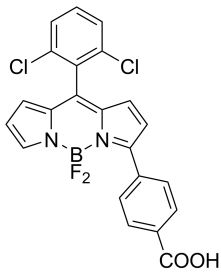
Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (134.8 mg, 0.4 mmol) and 2-nitrobenzenediazonium tetrafluoroborate **4.12c** (94.8 mg, 0.4 mmol) in acetone (3.2 mL). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (14.9 mg, 0.08 mmol in 0.8 mL acetone) over 24 minutes. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 4:6 v/v) providing an orange solid with a green luster (93.7 mg, 51%). Mp: transition at 208 °C, partial melting point of original crystals at 224 °C, partial melting point of new crystals at 245 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.23 (d, 1H, J = 8.1 Hz), 7.79-7.71 (m, 3H), 7.70-7.64 (m, 1H), 7.54-7.48 (m, 2H), 7.44 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.2 Hz), 6.78 (d, 1H, J = 4.1 Hz), 6.68 (d, 1H, J = 4.0 Hz), 6.49 (d, 1H, J = 4.1 Hz), 6.47 (d, 1H, J = 3.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.7, 148.5, 145.2, 140.3, 135.7, 135.5, 134.7, 132.9, 132.1, 131.5, 131.4, 130.7, 130.3, 129.7, 128.4, 127.8, 124.7, 120.6, 119.3 ppm; MS (EI, *m/z*): 457 (100%), 458 (40%), 459 (66%); HRMS (EI, *m/z*): calculated for $C_{21}H_{12}BCl_2F_2N_3O_2$ 457.03677, found 457.03592.

3-(4-Cyanophenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13d



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-cyanobenzenediazonium tetrafluoroborate **4.12d** (21.7 mg, 0.1 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 1:2 v/v) providing a purple solid with a green luster (32.5 mg, 74%). Mp: decomposition at 150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, 2H, J = 8.65 Hz), 7.94 (s, 1H), 7.77 (d, 2H, J = 8.65 Hz), 7.55-7.41 (m, 3H), 6.77-6.71 (m, 2H), 6.67 (d, 1H, J = 4.15 Hz), 6.56 (d, 1H, J = 4.15 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 146.0, 137.0, 136.4, 135.4, 134.8, 132.2, 131.5, 131.4, 130.5, 130.2, 130.1, 130.1, 128.5, 121.0, 120.0, 118.8, 113.3 ppm; MS (EI, *m/z*): 437; HRMS (EI, *m/z*): calculated for $C_{22}H_{12}BCl_2F_2N_3$ 437.04694, measured 437.04898.

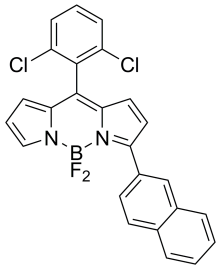
3-(4-Carboxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13e



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-carboxybenzenediazonium tetrafluoroborate **4.12e** (23.6 mg, 0.1 mmol). The crude

product was purified by column chromatography (silica; CH_2Cl_2 to CH_2Cl_2/ethyl acetate/acetic acid; 80:20:0.1 v/v/v). This was partially evaporated. Next, the solution was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness providing a purple solid with a green metallic luster (24.1 mg, 53%). Mp: transition at 232 °C, decomposition at 300 °C; ^{1}H NMR (THF-d_8, 300 MHz): δ 8.17-8.07 (m, 4H), 7.96 (s, 1H), 7.64-7.52 (m, 3H), 6.88 (d, 1H, J = 4.35 Hz), 6.82 (d, 1H, J = 4.30 Hz), 6.73 (d, 1H, J = 4.15 Hz), 6.56 (d, 1H, J = 4.15 Hz) ppm; ^{13}C NMR (THF-d_8, 75 MHz): δ 167.2, 160.3, 145.9, 140.0, 136.7, 136.0, 132.9, 132.6, 132.5, 131.4, 130.4, 130.4, 130.3, 130.2, 129.6, 129.3, 122.3, 120.0 ppm; MS (ESI, *m/z*): 608 (M + CH_2Cl_2 + CH_2Cl_2 - F), 876 (M + M - F - F); HRMS (ESI-TOF, *m/z*): $[M + H]^+$ calculated for $C_{22}H_{14}BCl_2F_2N_2O_2$ 457.0488, measured 457.0483; $[M - F]^+$ calculated for $C_{22}H_{13}BCl_2FN_2O_2$ 437.0431, measured 437.0426; $[M - H]^-$ calculated for $C_{22}H_{12}BCl_2F_2N_2O_2$ 455.0342, measured 455.0350; $[M - H - CO_2]^-$ calculated for $C_{21}H_{12}BCl_2F_2N_2$ 411.0439, measured 411.0449.

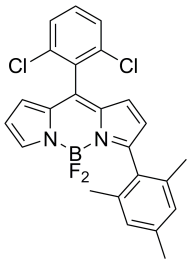
3-(2-Naphthyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13f



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and naphthalene-2-diazonium tetrafluoroborate **4.12f** (24.2 mg, 0.1 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing a purple solid with a copper luster (24.7 mg, 53%). Mp: decomposition at 125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.55 (s, 1H), 8.10 (dd, 1H, J_1 = 8.65 Hz, J_2 = 1.70 Hz), 8.01-7.92 (m, 2H), 7.91-7.84 (m, 2H), 7.60-7.40 (m, 5H), 6.84-6.76 (m, 2H), 6.64 (d, 1H, J = 3.95 Hz), 6.49 (d, 1H, J = 3.20 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75

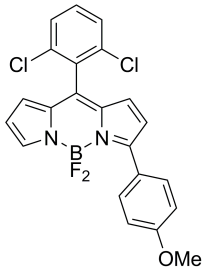
MHz): δ 161.6, 143.3, 137.4, 135.6, 134.1, 133.9, 133.1, 131.9, 131.3, 131.1, 130.3, 129.3, 128.4, 128.1, 128.0, 127.8, 127.6, 126.7, 126.5, 126.5, 126.4, 122.2, 118.7 ppm; MS (EI, *m/z*): 462 (100%), 463 (43%), 464 (66%); HRMS (EI, *m/z*): calculated for $C_{25}H_{15}BCl_2F_2N_2$ 462.06734, measured 462.06827.

3-Mesityl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13g



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 2,4,6-trimethylbenzenediazonium tetrafluoroborate **4.12g** (23.4 mg, 0.1 mmol). The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 6:4 v/v) providing an orange solid with a green luster (23.8 mg, 52%). Characterization data is described in the part about Chapter 1 (compound **1.9f**).

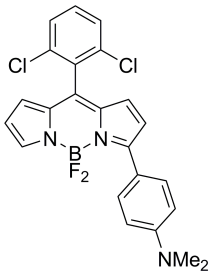
3-(4-Methoxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13h



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-methoxybenzenediazonium tetrafluoroborate **4.12h** (22.2 mg, 0.1 mmol). The crude

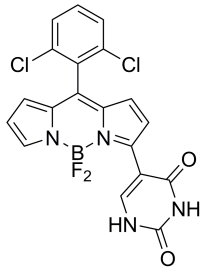
product was purified by column chromatography (silica; petroleum ether/diethyl ether; 7:3 v/v followed by silica; petroleum ether/diethyl ether; 2:1 v/v) providing dark crystals with a copper luster (18.2 mg, 41%). Characterization data is described in the part about Chapter 1 (compound **1.9b**).

3-(4-(Dimethylamino)phenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.13i



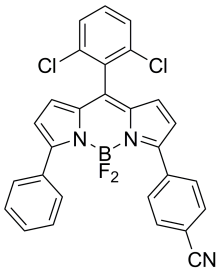
8-(2,6-Dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 4-(dimethylamino)benzenediazonium tetrafluoroborate **4.12i** (23.5 mg, 0.1 mmol) were dissolved in acetone (0.9 mL). To this reaction mixture was added dropwise, at room temperature, a decamethylferrocene solution (6.5 mg, 0.02 mmol in 0.2 mL CH_2Cl_2) over 6 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether/triethylamine; 66:34:0.1 v/v/v followed by silica; petroleum ether/CH_2Cl_2/triethylamine; 40:60:0.1 v/v/v) providing a green solid with a metallic luster (11.7 mg, 26%). Characterization data is described above in the part about diarylation.

3-(Uracil-5-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.15



Prepared according to the general procedure for radical C–H monoarylation using 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and uracil-5-diazonium tetrafluoroborate **4.12h** (22.6 mg, 0.1 mmol). The crude product was purified by column chromatography (silica; CH_2Cl_2/ethyl acetate; 7:3 v/v) providing a dark purple solid (12.3 mg, 28%). Mp: decomposition at 230 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 8.69-8.64 (m, 1H), 7.89 (s, 1H), 7.70-7.65 (m, 3H), 7.21 (d, 1H, J = 4.6 Hz), 6.90 (d, 1H, J = 4.5 Hz), 6.72 (d, 1H, J = 4.2 Hz), 6.58 (s, 1H) ppm; ^{13}C NMR (acetone-d_6, 150 MHz): δ 162.7, 155.9, 150.5, 146.3, 142.9, 138.2, 137.2, 135.7, 134.3, 132.9, 132.1, 131.7, 129.4, 128.0, 125.1, 119.1, 105.2 ppm; MS (ESI, *m/z*): 917 (M + M + Na^+); HRMS (ESI-TOF, *m/z*): $[M - F]^+$ calculated for $C_{19}H_{11}BCl_2FN_4O_2$ 427.0336, found 427.0331; $[M - H]^-$ calculated for $C_{19}H_{10}BCl_2F_2N_4O_2$ 445.0242, found 445.0255.

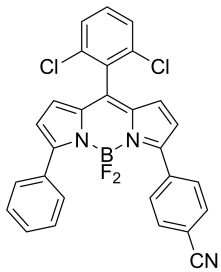
3-(4-Cyanophenyl)-5-phenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.16



3-Phenyl-BODIPY **4.13a** (41.3 mg, 0.1 mmol) and 4-cyanobenzenediazonium tetrafluoroborate **4.12d** (32.6 mg, 0.15 mmol) were dissolved in acetone (0.8 mL). To

this reaction mixture was added dropwise, at room temperature, a ferrocene solution (5.6 mg, 0.03 mmol in 0.2 mL aceton) over 9 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 1:1 v/v) providing a purple solid (12.2 mg, 24%). Mp: transition at 228 °C, melting point at 252 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 2H, J = 8.50 Hz), 7.96-7.89 (m, 2H), 7.71 (d, 2H, J = 8.65 Hz), 7.55-7.42 (m, 6H), 6.76 (d, 1H, J = 4.30 Hz), 6.69 (d, 1H, J = 4.35 Hz), 6.66 (d, 1H, J = 4.15 Hz), 6.60 (d, 1H, J = 4.15 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.4, 155.4, 138.1, 137.1, 137.0, 136.0, 135.7, 132.1, 131.9, 131.8, 131.4, 131.0, 130.6, 130.1, 130.1, 130.0, 129.8, 129.7, 129.7, 128.6, 128.4, 128.3, 122.9, 120.7, 118.9, 112.7 ppm; MS (EI, *m/z*): 513 (100%), 514 (47%), 515 (68%); HRMS (EI, *m/z*): calculated for $C_{28}H_{16}BCl_2F_2N_3$ 513.07824, measured 513.0792.

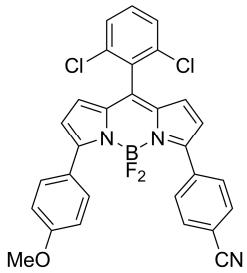
3-(4-Cyanophenyl)-5-phenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.16



3-(4-Cyanophenyl)-BODIPY **4.13d** (43.8 mg, 0.1 mmol) and benzenediazonium tetrafluoroborate **4.12a** (28.8 mg, 0.15 mmol) were dissolved in acetone (0.8 mL). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (5.6 mg, 0.03 mmol in 0.2 mL aceton) over 9 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered,

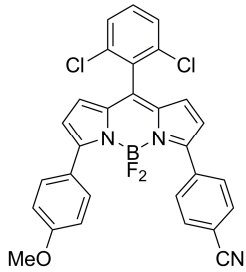
and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 4:6 v/v followed by silica; petroleum ether/ethyl acetate; 3:1 v/v) providing a purple solid (37.6 mg, 73%). Characterization data is described in the previous experiment.

3-(4-Cyanophenyl)-5-(4-methoxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.17



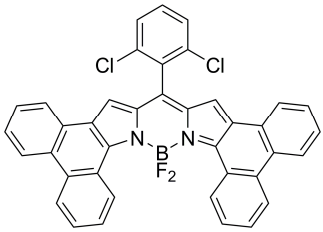
3-(4-Cyanophenyl)-BODIPY **4.13d** (43.8 mg, 0.1 mmol) and 4-methoxybenzenediazonium tetrafluoroborate **4.12h** (33.3 mg, 0.15 mmol) were dissolved in acetone (0.8 mL). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (5.6 mg, 0.03 mmol in 0.2 mL aceton) over 9 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 2:1 v/v) providing a blue solid with a green metallic luster (29.6 mg, 54%). Mp 295 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, 2H, J = 8.45 Hz), 7.96 (d, 2H, J = 8.85 Hz), 7.71 (d, 2H, J = 8.65 Hz), 7.55-7.40 (m, 3H), 6.99 (d, 2H, J = 9.05 Hz), 6.77-6.69 (m, 2H), 6.62-6.55 (m, 2H), 3.88 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.8, 161.9, 154.0, 137.5, 137.4, 136.7, 135.8, 135.6, 132.1, 131.9, 131.9, 131.8, 131.7, 131.3, 131.2, 130.1, 130.1, 130.0, 128.4, 127.1, 124.1, 123.1, 120.2, 119.0, 114.2, 112.4, 55.5 ppm; MS (EI, *m/z*): 543 (100%), 455 (47%), 545 (69%); HRMS (EI, *m/z*): calculated for $C_{29}H_{18}BCl_2F_2N_3O$ 543.0888, measured 543.08927.

3-(4-Cyanophenyl)-5-(4-methoxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.17



3-(4-Methoxyphenyl)-BODIPY **4.13h** (44.3 mg, 0.1 mmol) and 4-cyanobenzenediazonium tetrafluoroborate **4.12d** (32.6 mg, 0.15 mmol) were dissolved in acetone (0.8 mL). To this reaction mixture was added dropwise, at room temperature, a ferrocene solution (5.6 mg, 0.03 mmol in 0.2 mL aceton) over 9 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the diazonium salt. Next, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 1:2 v/v) providing a blue solid with a green metallic luster (19.3 mg, 36%). Characterization data is described in the previous experiment.

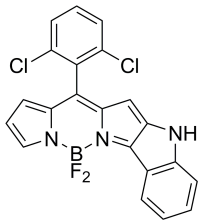
8-(2,6-Dichlorophen-1-yl)-4,4-difluoro-diphenanthro[9,10-*b*,*g*](4-bora-3a,4a-diaza-*s*-indacene) 4.18



3,5-Bis(biphenyl-2-yl)-BODIPY **4.10k** (64.1 mg, 0.1 mmol) was dissolved in DCM (20 mL) and this solution was cooled to -78 °C. Once cooled, $BF_3{\cdot}OEt_2$ (50 µL, 0.4 mmol, 4 equivalents) was added dropwise followed by dropwise addition of a PIFA (172.0 mg, 0.4 mmol, 4 equivalents) solution in DCM (2 mL). The reaction mixture

was stirred at -78 °C for 2 hours followed by 1 hour at -20 °C. Afterwards, the reaction was quenched with MeOH (20 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (18 mL). After stirring 5 minutes at room temperature, the solution was poured in DCM (250 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; heptane/CH_2Cl_2; 1:1 v/v) providing a dark blue solid with a green metallic luster (41.9 mg, 66%). Mp >340 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.67 (d, 2H, J = 7.9 Hz), 8.58 (d, 2H, J = 8.4 Hz), 8.47 (d, 2H, J = 7.5 Hz), 7.99 (d, 2H, J = 9.0 Hz), 7.86-7.70 (m, 4H), 7.67-7.58 (m, 3H), 7.56-7.45 (m, 4H), 7.30 (s, 2H) ppm; ^{13}C NMR: product is too insoluble to obtain a fully resolved spectrum; MS (ESI, *m/z*): 1297 (M + M + Na^+).

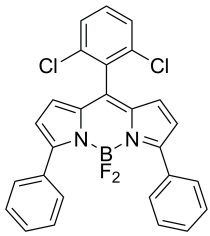
8-(2,6-Dichlorophen-1-yl)-4,4-difluoro-indolo[2,3-*b*](4-bora-3a,4a-diaza-*s*-indacene) 4.19



3-(2-Nitrophenyl)-BODIPY **4.13c** (45.8 mg, 0.1 mmol) was dissolved in 1,2-dichlorobenzene (0.2 mL) and to this solution was added $P(OEt)_3$ (0.2 mL, 1.2 mmol, 12 equivalents). The reaction vessel was then flushed with nitrogen and the reaction mixture was heated in a microwave at 180 °C (300 W) for 40 minutes. Upon completion, the reaction mixture was cooled to room temperature, poured in diethyl ether (100 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), with saturated aqueous NaCl (10O mL) and with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 1:2 v/v) providing a purple solid with a green metallic luster (11.0 mg, 26%). Mp 245 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.20 (d, 1H, J = 8.0 Hz), 7.78 (s, 1H), 7.48 (d, 2H, J = 8.1 Hz), 7.44-7.37 (m, 2H), 7.20-7.12 (m, 3H), 6.45 (s, 1H), 6.41 (s, 1H), 6.01 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ

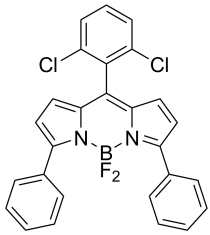
150.8, 140.8, 135.8, 132.2, 131.7, 131.1, 128.3, 125.9, 125.7, 121.61, 117.1, 114.8, 112.2, 103.1 ppm (due to the poor solubility of the product not all carbon peaks are resolved); MS (EI, *m/z*): 425 (100%), 426 (42%), 427 (66%); HRMS (EI, *m/z*): calculated for $C_{21}H_{12}BCl_2F_2N_3$ 425.04694, found 425.04543.

3,5-Diphenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10a



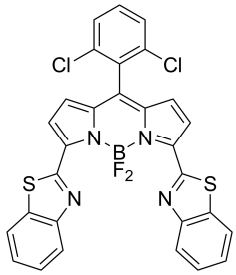
Aniline **4.20** (23.0 µL, 0.25 mmol, 2.5 equivalents) was dissolved in DCM (0.2 mL) and this solution was cooled in an ice bath. Then $BF_3{\cdot}OEt_2$ (46 µL, 0.375 mmol, 3.75 equivalents) and *tert*-butyl nitrite (35.5 µL, 0.3 mmol, 3 equivalents) were added and the reaction mixture was stirred for one hour at 0 °C. Afterwards, the reaction was brought to room temperature. Next, 8-(2,6-dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol, 1 equivalent) and aceton (0.7 mL) were added. And to this reaction mixture was added dropwise, at room temperature, a ferrocene solution (9.3 mg, 0.05 mmol in 0.2 mL acetone) over 15 minutes. After the addition, the reaction mixture was stirred at the same temperature until IR analysis showed complete consumption of the intermediate diazonium salt. Finally, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing a purple solid with a copper luster (25.8 mg, 53%). Characterization data is described in the part about Chapter 1 (compound **1.10a**).

3,5-Diphenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.10a



8-(2,6-Dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) was dissolved in DMSO (1 mL). To this solution were added aniline **4.20** (23.0 µL, 0.25 mmol, 2.5 equivalents), $BF_3{\cdot}OEt_2$ (46 µL, 0.375 mmol, 3.75 equivalents) and *tert*-butyl nitrite (35.5 µL, 0.3 mmol, 3 equivalents) and the reaction mixture was stirred at room temperature for 5.5 hours. Afterwards, the reaction poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; heptane/CH_2Cl_2; 2:1 v/v) providing a purple solid with a copper luster (30.5 mg, 62%). Characterization data is described in the part about Chapter 1 (compound **1.10a**).

3,5-Di(benzo[*d*]thiazol-2-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 4.23



8-(2,6-Dichlorophenyl)-BODIPY **4.8a** (33.7 mg, 0.1 mmol) and 2-aminobenzothiazole **4.21** (37.6 mg, 0.25 mmol, 2.5 equivalents) were dissolved in DMSO (1 mL). To this solution were added $BF_3{\cdot}OEt_2$ (46 µL, 0.375 mmol, 3.75 equivalents) and *tert*-butyl nitrite (35.5 µL, 0.3 mmol, 3 equivalents) and the reaction mixture was stirred at room temperature for 6 hours. Afterwards, the reaction poured

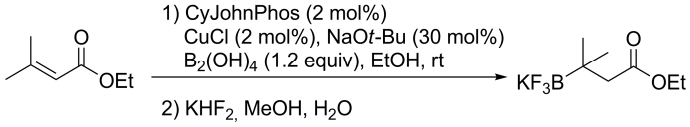
in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; heptane/CH_2Cl_2; 1:2 v/v) providing the desired diaryl product **4.23** (8.1 mg, 13%) together with the monoarylated side product **4.22** (14.3 mg, 30%).

4.22: Dark purple solid; Mp: 135 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.15 (d, 1H, *J* = 8.2 Hz), 8.05 (s, 1H), 7.98 (d, 1H, *J* = 8.0 Hz), 7.56-7.49 (m, 3H), 7.48-7.40 (m, 3H), 6.75 (d, 1H, *J* = 3.9 Hz), 6.74 (d, 1H, *J* = 4.2 Hz), 6.60 (d, 1H, *J* = 3.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.5, 153.4, 151.0, 146.9, 140.0, 137.6, 137.5, 135.5, 135.4, 131.6, 131.4, 130.3, 129.5, 128.5, 126.8, 126.5, 124.1, 122.8, 121.8, 120.5 ppm; MS (EI, *m/z*): 469 (100%), 470 (33%), 471 (68%); HRMS (EI, *m/z*): calculated for $C_{22}H_{12}BCl_2F_2N_3S$ 469.01901, found 469.02072.

4.23: Dark blue solid; Mp transition at 295 °C, decomposition at 311 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, 2H, *J* = 7.9 Hz), 8.04 (d, 2H, *J* = 7.9 Hz), 7.57-7.45 (m, 9H), 6.77 (d, 2H, *J* = 4.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4, 153.4, 152.0, 138.5, 138.0, 135.7, 131.6, 131.5, 129.3, 128.5, 127.7, 126.9, 126.6, 124.2, 124.1, 121.9 ppm; MS (ESI, *m/z*): 1229 (M + M + Na^+); HRMS (ESI-TOF, *m/z*: [M + H]$^+$ calculated for $C_{29}H_{16}BCl_2F_2N_4S_2$ 603.0255, found 603.0258; [M - F]$^+$ calculated for $C_{29}H_{15}BCl_2FN_4S_2$ 583.0192, found 583.0224.

5. Synthetic procedures and characterization data from Chapter 5

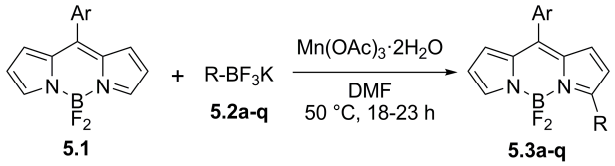
Potassium ethyl 3-(trifluoroborato)-3-methylbutanoate 5.2l



Synthesized according to literature procedure for β-trifluoroboration of carbonyl compounds.[7] A flask was charged with CuCl (9.9 mg, 0.1 mmol, 2 mol%), CyJohnPhos (35.0 mg, 0.1 mmol, 2 mol%), bisboronic acid (537.9 mg, 6 mmol, 1.2 equivalents) and NaOt-Bu (144.2 mg, 1.5 mmol, 30 mol%), this was 3 times evacuated and purged with argon. EtOH (50 mL) and ethyl 3,3-dimethylacrylate (0.7 mL, 5 mmol, 1 equivalent) were added *via* syringe and the mixture was stirred for 21

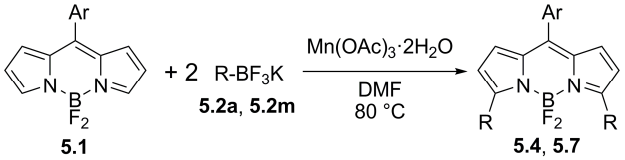
h. The reaction mixture was filtered through a plug of Celite, which was subsequently rinsed with EtOAc (3 x 40 mL). The filtrate was concentrated, and the resultant oil was dissolved in MeOH (50 mL). This solution was cooled in an ice-bath as an aqueous saturated KHF_2 (42.5 mmol) solution was added dropwise. The mixture was warmed to room temperature and was stirred for 3.5 h and evaporated to dryness. The resultant solid was triturated in cold acetone followed by warm acetone and filtered. The solution was subsequently concentrated to a minimal volume. To this solution was added dropwise Et_2O until the trifluoroborate precipitated. The mixture was filtered, washed with cold Et_2O and dried to yield the desired β-trifluoroborato ester **5.2l** as white crystals (591.0 mg, 50%). Mp 139-140 °C; ^{1}H NMR (DMSO-d_6, 300 MHz,): δ 3.95 (q, 2H, J = 7.10 Hz), 1.95 (s, 2H), 1.14 (t, 3H, J = 7.15 Hz), 0.68 (s, 6H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 174.2, 58.2, 43.1, 23.6, 14.5 ppm; ^{19}F NMR (DMSO-d_6, 565 MHz): δ -151.9 ppm; ^{11}B NMR (DMSO-d_6, 192 MHz): δ 4.94 ppm; HRMS (ESI-TOF, *m/z*): $[M - K]^-$ calculated for $C_7H_{13}BF_3O_2$ 197.0961, found 197.0972.

General radical C–H monofunctionalization procedure



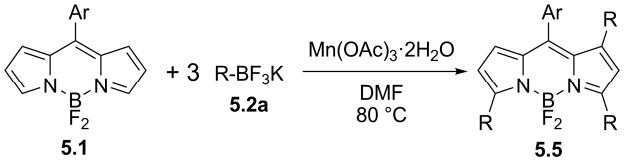
BODIPY **5.1** (0.1 mmol), organoboron compound **5.2a-q** (0.1 mmol, 1 equiv) and $Mn(OAc)_3{\cdot}2H_2O$ (0.25 mmol, 2.5 equiv) were dissolved in DMF (1 mL). The reaction mixture was heated at 50 °C and stirred for the indicated time. Upon completion, this was cooled to room temperature. Subsequently, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified chromatographically.

General radical C–H difunctionalization procedure



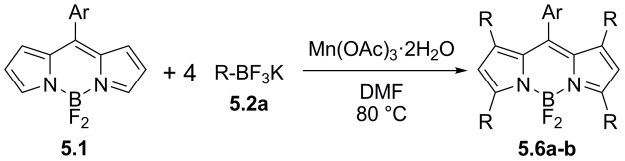
BODIPY **5.1** (0.1 mmol), potassium trifluoroborate **5.2a** or **5.2m** (0.2 mmol, 2 equiv) and $Mn(OAc)_3{\cdot}2H_2O$ (0.5 mmol, 5 equiv) were dissolved in DMF (1 mL). The reaction mixture was heated at 80 °C and stirred for the indicated time. Upon completion, this was cooled to room temperature. Subsequently, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified chromatographically.

General radical C–H trialkylation procedure



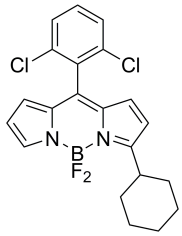
BODIPY **5.1** (0.1 mmol), potassium trifluoroborate **5.2a** (0.3 mmol, 3 equiv) and $Mn(OAc)_3{\cdot}2H_2O$ (0.75 mmol, 7.5 equiv) were dissolved in DMF (1 mL). The reaction mixture was heated at 80 °C and stirred for the indicated time. Upon completion, this was cooled to room temperature. Subsequently, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified chromatographically.

General radical C–H tetraalkylation procedure



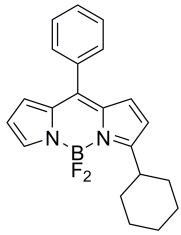
BODIPY **5.1** (0.1 mmol), potassium trifluoroborate **5.2a** (0.45 mmol, 4.5 equiv) and $Mn(OAc)_3 \cdot 2H_2O$ (1.1 mmol, 11 equiv) were dissolved in DMF (2 mL). The reaction mixture was heated at 80 °C and stirred for the indicated time. Upon completion, this was cooled to room temperature. Subsequently, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified chromatographically.

3-Cyclohexyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3a



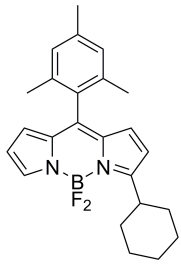
Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (19.0 mg, 0.1 mmol). This reaction was completed after 23 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 6:4 v/v) providing orange crystals with a green luster (32.2 mg, 77%). Mp 195 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (s, 1H), 7.51-7.33 (m, 3H), 6.65 (d, 1H, J = 4.30 Hz), 6.51 (d, 1H, J = 3.60 Hz), 6.43 (d, 2H, J = 4.55 Hz), 3.34 (t, 1H, J = 10.85 Hz), 2.11 (d, 2H, J = 11.30 Hz), 1.92-1.73 (m, 3H), 1.61-1.22 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7, 141.1, 137.9, 135.5, 135.2, 133.1, 131.8, 131.7, 131.1, 128.3, 126.6, 118.7, 117.3, 38.7, 32.5, 26.0, 26.0 ppm; MS (EI, *m/z*): 418; HRMS (EI, *m/z*): calculated for $C_{21}H_{19}BCl_2F_2N_2$ 418.09864, found 418.09765.

3-Cyclohexyl-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3b



Prepared according to the general radical C–H monofunctionalization procedure using 8-phenyl-BODIPY **5.1b** (26.8 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (19.0 mg, 0.1 mmol). This reaction was completed after 19 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 6:4 v/v) providing an orange solid with a green luster (20.9 mg, 60%). Mp 48 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (s, 1H), 7.60-7.44 (m, 5H), 6.90 (d, 1H, J = 4.50 Hz), 6.75 (d, 1H, J = 3.80 Hz), 6.46 (d, 2H, J = 4.15 Hz), 3.34 (t, 1H, J = 11.30 Hz), 2.08 (d, 2H, J = 12.00 Hz), 1.92-1.74 (m, 3H), 1.54-1.27 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 171.1, 144.7, 140.4, 135.1, 134.3, 133.8, 133.4, 130.5, 130.3, 128.4, 117.9, 117.0, 38.5, 32.7, 26.1, 26.1 ppm (one carbon overlap); MS (EI, *m/z*): 350; HRMS (EI, *m/z*): calculated for $C_{21}H_{21}BF_2N_2$ 350.17659, found 350.1773.

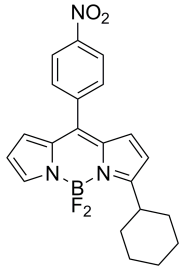
3-Cyclohexyl-8-mesityl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3c



Prepared according to the general radical C–H monofunctionalization procedure using 8-mesityl-BODIPY **5.1c** (31.0 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (19.0 mg, 0.1 mmol). This reaction was completed after 19.5 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing an orange solid with a green luster (19.7

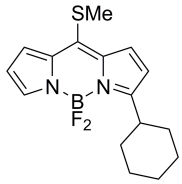
mg, 50%). Mp: decomposition at 53 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (s, 1H), 6.93 (s, 2H), 6.64 (d, 1H, J = 4.35 Hz), 6.50 (d, 1H, J = 3.40 Hz), 6.38 (d, 2H, J = 4.15 Hz), 3.32 (t, 1H, J = 10.90 Hz), 2.35 (s, 3H), 2.19-2.01 (m, 8H), 1.92-1.73 (m, 3H), 1.53-1.27 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 171.2, 144.6, 140.3, 138.6, 136.7, 135.6, 134.0, 131.9, 130.2, 128.2, 126.9, 117.8, 116.9, 38.6, 32.7, 26.1, 26.1, 21.3, 20.2 ppm; MS (EI, *m/z*): 392; HRMS (EI, *m/z*): calculated for $C_{24}H_{27}BF_2N_2$ 392.22354, found 392.22222.

3-Cyclohexyl-8-(4-nitrophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3d



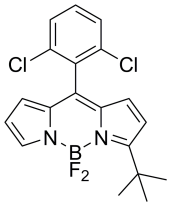
Prepared according to the general radical C–H monofunctionalization procedure using 8-(4-nitrophenyl)-BODIPY **5.1d** (31.3 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (19.0 mg, 0.1 mmol). This reaction was completed after 18.5 hours. The crude product was purified by column chromatography (silica; heptane/CH_2Cl_2; 4:6 v/v) providing an orange solid with a green luster (22.7 mg, 58%). Mp: transition at 194 °C, melting point at 214 °C; 1H NMR ($CDCl_3$, 300 MHz): δ 8.37 (d, 2H, J = 8.15 Hz), 7.81 (s, 1H), 7.71 (d, 2H, J = 8.45 Hz), 6.79 (d, 1H, J = 4.55 Hz), 6.65 (d, 1H, J = 3.95 Hz), 6.55-6.45 (m, 2H), 3.35 (t, 1H, J = 11.20 Hz), 2.07 (d, 2H, J = 11.85 Hz), 1.92-1.75 (m, 3H), 1.53-1.27 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.8, 149.0, 141.5, 141.1, 140.5, 134.8, 133.2, 132.8, 131.3, 127.9, 123.7, 118.9, 117.8, 38.7, 32.6, 26.0, 26.0 ppm; MS (EI, *m/z*): 395 (M), 375 (M - HF); HRMS (ESI-TOF, *m/z*): $[M + H]^+$ calculated for $C_{21}H_{21}BF_2N_3O_2$ 396.1695, found 396.1688; $[M - F]^+$ calculated for $C_{21}H_{20}BFN_3O_2$ 376.1633, found 376.1628; $[M]^-$ calculated for $C_{21}H_{20}BF_2N_3O_2$ 395.1617, found 395.1628.

3-Cyclohexyl-8-methylthio-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3e



Prepared according to the general radical C–H monofunctionalization procedure using 8-methylthio-BODIPY **5.1e** (23.8 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (19.0 mg, 0.1 mmol). This reaction was completed after 18.5 hours. The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 3:1 v/v) providing an orange solid with a green luster (14.0 mg, 44%). Mp: product is not crystalline; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (s, 1H), 7.47 (d, 1H, J = 4.30 Hz), 7.30-7.25 (m, 1H), 6.50-6.42 (m, 2H), 3.26 (t, 1H, J = 11.40 Hz), 2.79 (s, 3H), 2.05 (d, 2H, J = 11.45 Hz), 1.89-1.72 (m, 3H), 1.51-1.26 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.8, 148.1, 138.9, 135.6, 133.5, 130.5, 125.7, 117.4, 116.7, 38.4, 32.7, 26.1, 26.1, 21.2 ppm; MS (EI, *m/z*): 320; HRMS (EI, *m/z*): calculated for $C_{16}H_{19}BF_2N_2S$ 320.13301, found 320.13320.

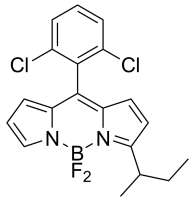
3-Tert-butyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3g



Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium tert-butyltrifluoroborate **5.2g** (16.4 mg, 0.1 mmol). This reaction was completed after 19 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 6:4 v/v) providing an orange solid with a green luster (23.5 mg, 60%). Mp 160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (s, 1H), 7.51-7.36 (m, 3H), 6.63 (d, 1H, J = 4.50 Hz), 6.55 (d, 1H, J = 3.95 Hz), 6.50 (d, 1H, J = 4.55 Hz), 6.45 (d, J = 3.95 Hz), 1.56 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.8, 142.2, 138.5,

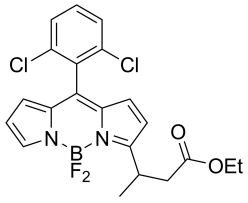
137.5, 135.6, 133.0, 132.0, 131.6, 131.1, 128.3, 127.0, 119.8, 118.0, 35.5, 30.5 ppm; MS (EI, *m/z*): 392; HRMS (EI, *m/z*): calculated for $C_{19}H_{17}BCl_2F_2N_2$ 392.08299, found 392.08424.

3-Sec-butyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3h



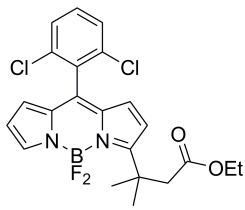
Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium sec-butyltrifluoroborate **5.2h** (16.4 mg, 0.1 mmol). This reaction was completed after 19 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 6:4 v/v) providing an orange solid with a green luster (29.8 mg, 76%). Mp 135 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (s, 1H), 7.52-7.34 (m, 3H), 6.68 (d, 1H, J = 4.55 Hz), 6.52 (d, 1H, J = 3.75 Hz), 6.42 (d, 2H, J = 4.30 Hz), 3.46 (sex, 1H, J = 6.85 Hz), 1.84-1.60 (m, 2H), 1.34 (d, 3H, J = 6.80), 0.97 (t, 3H, J = 7.40 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 141.1, 137.9, 135.6, 135.2, 133.1, 131.9, 131.7, 131.1, 128.3, 126.6, 118.2, 117.3, 35.6, 29.8, 20.1, 12.1 ppm; MS (EI, *m/z*): 392 (100%), 393 (38%), 394 (66%); HRMS (EI, *m/z*): calculated for $C_{19}H_{17}BCl_2F_2N_2$ 392.08299, found 392.08292.

3-(4-Ethoxy-4-oxobutan-2-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3k



Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium ethyl 3-(trifluoroborato)-butanoate **5.2k** (22.2 mg, 0.1 mmol). This reaction was completed after 20 hours. The crude product was purified by column chromatography (silica; CH_2Cl_2) providing an orange solid with a green luster (22.8 mg, 51%). Mp: product is not crystalline; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (s, 1H), 7.51-7.36 (m, 3H), 6.66 (d, 1H, J = 4.55 Hz), 6.57 (d, 1H, J = 3.95 Hz), 6.48-6.40 (m, 2H), 4.13 (q, 2H, J = 7.10 Hz), 4.02 (sex, 1H, J = 7.15 Hz), 2.83 (dd, 1H, J_1 = 15.35 Hz, J_2 = 6.30 Hz), 2.61 (dd, 1H, J_1 = 15.45 Hz, J_2 = 8.30 Hz), 1.43 (d, 3H, J = 6.95 Hz), 1.20 (t, 3H, J = 7.15 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 169.5, 142.5, 138.8, 135.5, 135.5, 135.1, 133.6, 131.7, 131.4, 131.2, 128.3, 127.6, 118.0, 117.9, 60.8, 41.0, 30.7, 29.8, 20.0, 14.3 ppm; MS (EI, *m/z*): 450 (M), 430 (M - HF); HRMS (EI, *m/z*): calculated for $C_{21}H_{19}BCl_2F_2N_2O$ 450.08847, found 450.08774.

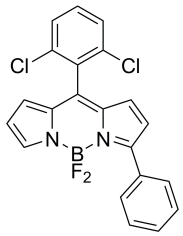
3-(4-Ethoxy-2-methyl-4-oxobutan-2-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3l



Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium ethyl 3-(trifluoroborato)-3-methylbutanoate **5.2l** (23.6 mg, 0.1 mmol). This reaction was completed after 18.5 hours. The crude product was purified by column chromatography (silica; CH_2Cl_2) providing an orange solid with a green luster (26.7 mg, 57%). Mp: product is not crystalline; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (s, 1H), 7.50-7.35 (m, 3H), 6.65 (d, 1H, J = 4.50 Hz), 6.55 (d, 2H, J = 4.15 Hz), 6.47-6.42 (m, 1H), 4.02 (q, 2H, J = 7.15 Hz), 3.13 (s, 2H), 1.61 (s, 6H), 1.13 (t, 3H, J = 7.15 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.7, 171.6, 142.1, 137.5, 135.5, 133.0, 132.0, 131.5, 131.1, 128.3, 127.0, 120.8, 118.1, 60.3, 46.1, 37.0, 29.8, 29.2,

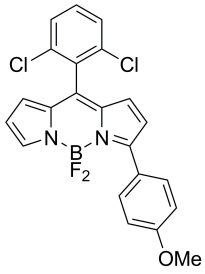
14.2 ppm; MS (EI, *m/z*): 464; HRMS (EI, *m/z*): calculated for $C_{22}H_{21}BCl_2F_2N_2O_2$ 464.10412, found 464.10427.

3-Phenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3m



Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium phenyltrifluoroborate **5.2m** (18.4 mg, 0.1 mmol). This reaction was completed after 22.5 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 6:4 v/v) providing red crystals with a green luster (17.4 mg, 42%). Characterization data is described in the part about Chapter 1 (compound **1.9a**).

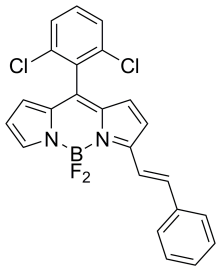
3-(4-Methoxyphenyl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3n



Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium 4-methoxy-phenyltrifluoroborate **5.2n** (21.4 mg, 0.1 mmol). This reaction was completed after 18 hours. The crude product was purified by column chromatography (silica; petroleum ether/diethyl ether; 7:3 v/v) providing dark purple crystals with a

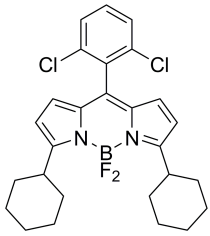
copper luster (18.5 mg, 42%). Characterization data is described in the part about Chapter 1 (compound **1.9b**).

3-Phenylethenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3p



Prepared according to the general radical C–H monofunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium trans-β-styryltrifluoroborate **5.2p** (21.0 mg, 0.1 mmol). This reaction was completed after 19 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 6:4 v/v). The resulting cis/trans mixture was separated *via* crystallization from a heptane/dichloromethane mixture by evaporation followed by filtering and washing the formed crystals with pentane. This provided the pure trans compound as a purple solid with a green metallic luster (8.6 mg, 20 %). Data are in full accordance with the literature.[1]

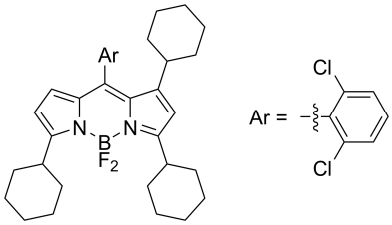
3,5-Dicyclohexyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.4



Prepared according to the general radical C–H difunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (38.0 mg, 0.2 mmol). This reaction was completed

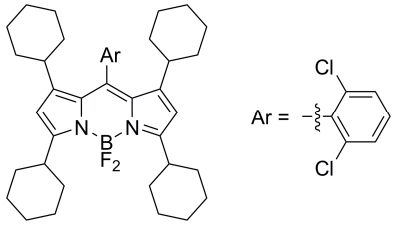
after 2 hours. The crude product was purified by column chromatography (silica; petroleum ether/ethyl acetate; 97:3 v/v) providing an orange solid with a green luster (46.1 mg, 92%). Mp 207 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47-7.31 (m, 3H), 6.48 (d, 2H, J = 4.15 Hz), 6.33 (d, 2H, J = 4.30 Hz), 3.31 (t, 2H, J = 11.50 Hz), 2.10 (d, 4H, J = 11.85 Hz), 1.89-1.72 (m, 6H), 1.60-1.18 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.3, 136.0, 135.7, 133.2, 132.2, 130.8, 128.6, 128.2, 116.5, 38.3, 33.1, 26.2, 26.2 ppm; MS (EI, *m/z*): 500 (M, 100%), 501 (M, 47%), 502 (M, 68%), 480 (M - HF); HRMS (EI, *m/z*): calculated for $C_{27}H_{29}BCl_2F_2N_2$ 500.17689, found 500.17851.

1,3,5-Tricyclohexyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.5



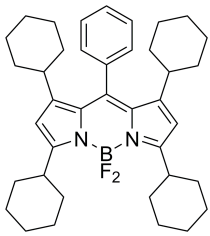
Prepared according to the general radical C–H trialkylation procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (57.0 mg, 0.3 mmol). This reaction was completed after 3 hours. The crude product was purified by column chromatography (silica; petroleum ether/ethyl acetate; 98:2 v/v, followed by silica; petroleum ether/ethyl acetate; 99:1 v/v) providing an orange solid with a green luster (33.1 mg, 57%). Mp. 231 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49-7.34 (m, 3H), 6.30 (d, 1H, J = 4.15 Hz), 6.25 (s, 1H, J = 4.15 Hz), 6.22 (s, 1H), 3.40-3.18 (m, 2H), 2.09 (d, 4H, J = 11.85 Hz), 1.89-1.71 (m, 6H), 1.66-1.57 (m, 3H), 1.55-1.28 (m, 12H), 1.21-0.97 (m, 4H), 0.75-0.57 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 165.4, 154.5, 135.8, 135.3, 133.2, 132.7, 130.7, 129.7, 128.1, 127.3, 126.9, 115.0, 38.2, 38.1, 37.1, 34.4, 33.3, 32.9, 27.0, 26.3, 26.2, 26.2, 26.2, 25.9 ppm; MS (EI, *m/z*): 582 (100%), 583 (50%), 584 (68%); HRMS (EI, *m/z*): calculated for $C_{33}H_{39}BCl_2F_2N_2$ 582.25514, found 582.25514.

1,3,5,7-Tetracyclohexyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.6a



Prepared according to the general radical C–H tetraalkylation procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (85.5 mg, 0.45 mmol). This reaction was completed after 19.5 hours. The crude product was purified by column chromatography (silica; petroleum ether/ethyl acetate; 99:1 v/v) providing an orange solid with a green luster (35.0 mg, 53%). Mp: transition at 260 °C, melting point at 325 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.42 (m, 3H), 6.18 (s, 2H), 3.28 (t, 2H, J = 11.60 Hz), 2.07 (d, 4H, J = 11.65 Hz), 1.87-1.71 (m, 6H), 1.65-1.57 (m, 5H), 1.54-1.27 (m, 13H), 1.24-0.97 (m, 10H), 0.74-0.55 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.3, 153.1, 136.3, 135.6, 134.1, 130.9, 128.4, 128.1, 114.3, 38.0, 37.1, 34.9, 33.2, 27.1, 26.3, 26.0 ppm (one carbon overlap); MS (EI, *m/z*): 664 (100%), 665 (55%), 666 (74%); HRMS (EI, *m/z*): calculated for $C_{39}H_{49}BCl_2F_2N_2$ 664.33339, found 664.33365.

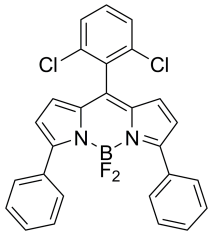
1,3,5,7-Tetracyclohexyl-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.6b



Prepared according to the general radical C–H tetraalkylation procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium cyclohexyltrifluoroborate **5.2a** (85.5 mg, 0.45 mmol). This reaction was completed after 3.5 hours. The crude product was purified by column chromatography (silica;

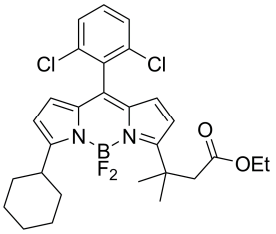
petroleum ether/CH_2Cl_2; 3:1 v/v) providing a yellow solid (35.4 mg, 59%). Mp 342 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57-7.49 (m, 1H), 7.47-7.34 (m, 4H), 6.15 (s, 2H), 3.27 (t, J = 11.70 Hz, 2H), 2.03 (d, J = 12.05 Hz, 4H), 1.87-1.70 (m, 6H), 1.55-1.17 (m, 20H), 1.14-0.92 (m, 8H), 0.69-0.48 ppm (m, 4H); 13C NMR ($CDCl_3$, 75 MHz): δ 165.5, 154.7, 141.7, 135.7, 129.5, 128.8, 128.7, 128.2, 114.1, 37.9, 36.2, 34.9, 33.2, 26.7, 26.3, 26.0 ppm (one carbon overlap); MS (EI, *m/z*): 597; HRMS (EI, *m/z*): calculated for $C_{39}H_{51}BF_2N_2$ 596.41134, found 596.41287.

3,5-Diphenyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.7



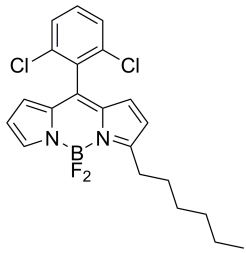
Prepared according to the general radical C–H difunctionalization procedure using 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol) and potassium phenyltrifluoroborate **5.2m** (36.8 mg, 0.2 mmol). This reaction was completed after 21.5 hours. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 2:1 v/v) providing purple crystals with a copper luster (9.2 mg, 19%). Characterization data is described in the part about Chapter 1 (compound **1.10a**).

3-Cyclohexyl-5-(4-ethoxy-2-methyl-4-oxobutan-2-yl)-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.8



3-Cyclohexyl-BODIPY **5.3a** (41.9 mg, 0.1 mmol, 1 equiv), potassium ethyl 3-(trifluoroborato)-3-methylbutanoate **5.2l** (23.6 mg, 0.1 mmol, 1 equiv) and $Mn(OAc)_3 \cdot 2H_2O$ (67.0 mg, 0.25 mmol, 2.5 equiv) were dissolved in DMF (1 mL). The reaction mixture was heated at 80 °C and stirred for 40 minutes. Upon completion, this was cooled to room temperature. Subsequently, the crude mixture was poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; petroleum ether/CH_2Cl_2; 1:1 v/v) providing an orange solid (41.7 mg, 76%). Mp 147 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.32 (m, 3H), 6.51 (d, 1H, J = 4.35 Hz), 6.46 (d, 1H, J = 4.35 Hz), 6.42 (d, 1H, J = 4.15 Hz), 6.38 (d, 1H, J = 4.15 Hz), 4.02 (q, 2H, J = 7.15 Hz), 3.34 (t, 1H, J = 11.10 Hz), 3.10 (s, 2H), 2.10 (d, 2H, J = 11.65 Hz), 1.89-1.73 (m, 3H), 1.61 (s, 6H), 1.54-1.23 (m, 5H), 1.12 (t, 3H, J = 7.05 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, 169.6, 168.4, 136.4, 135.8, 135.5, 132.4, 130.9, 128.9, 128.2, 128.0, 118.5, 117.7, 60.1, 46.3, 46.3, 38.2, 36.8, 32.9, 29.4, 26.2, 26.1, 14.3 ppm; MS (EI, *m/z*): 546; HRMS (EI, *m/z*): calculated for $C_{28}H_{31}BCl_2F_2N_2O_2$ 546.18237, found 546.18194.

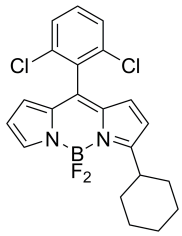
3-*n*-Hexyl--8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.11



1-Hexene **5.9** (37.0 µL, 0.3 mmol, 3 equivalents) was brought under a nitrogen atmosphere and dissolved in dry THF (0.1 mL). This solution was cooled in an ice bath and to this was added dropwise $BH_3 \cdot$THF (0.1 mL of 1.0 M solution in THF, 0.1 mmol, 1 equivalent). Next, this reaction was stirred at room temperature for one hour. Afterwards, a solution of 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol, 1 equivalent) in DMSO (0.9 mL) was added and air was bubbled through the reaction mixture at room temperature for 4.5 hours. The reaction was then poured in diethyl

ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; heptane/CH_2Cl_2; 2:1 v/v) providing a red sticky solid with a green luster (11.0 mg, 26%). Mp: product is not crystalline °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (s, 1H), 7.50-7.34 (m, 3H), 6.65 (d, 1H, J = 4.3 Hz), 6.52 (d, 1H, J = 3.4 Hz), 6.45-6.36 (m, 2H), 3.06 (t, 2H, J = 7.9 Hz), 1.85-1.70 (m, 2H), 1.53-1.44 (m, 2H), 1.38-1.32 (m, 4H), 0.93-0.87 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 141.5, 141.1, 137.9, 135.5, 133.3, 131.8, 131.5, 131.1, 128.3, 126.9, 120.4, 117.5, 31.7, 29.8, 29.5, 28.3, 22.7, 14.2 ppm; MS (EI, *m/z*): 420 (100%), 421 (40%), 422 (67%); HRMS (EI, *m/z*): calculated for $C_{21}H_{21}BCl_2F_2N_2$ 420.11429, found 420.11300.

3-Cyclohexyl-8-(2,6-dichlorophen-1-yl)-4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene 5.3a



Cyclohexene (30.5 µL, 0.3 mmol, 3 equivalents) was brought under a nitrogen atmosphere and dissolved in dry THF (0.1 mL). This solution was cooled in an ice bath and to this was added dropwise BH_3·THF (0.1 mL of 1.0 M solution in THF, 0.1 mmol, 1 equivalent). Next, this reaction was stirred at room temperature for one hour. Afterwards, a solution of 8-(2,6-dichlorophenyl)-BODIPY **5.1a** (33.7 mg, 0.1 mmol, 1 equivalent) in DMSO (0.9 mL) was added and air was bubbled through the reaction mixture at room temperature for 5 hours. The reaction was then poured in diethyl ether (100 mL), washed three times with water (100 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by column chromatography (silica; heptane/CH_2Cl_2; 6:4 v/v) providing orange crystals with a green luster (11.5 mg, 27%). Characterization data is described above with the trifluoroborate procedure.

6. Safety aspects

All experimental work performed throughout this thesis was executed in compliance of the code of practice for safety in the lab,[8] and the departmental safety brochure.[9] Specific information regarding personal protection and precautions can be found at the KU Leuven HSE (Health, Safety and Environment) website[10] and the departmental risk assessment SharePoint.[11] All reactions were done in a ventilated fume hood while using protective gloves, a lab-coat and safety glasses. Special precautions were taken when handling the following dangerous compounds.

Silver(I) oxide (Ag_2O)

Silver(I) oxide is a strong oxidizer, contact with combustible materials may cause a fire and contact with skin causes irritation and possibly burns, especially if the skin is wet or moist. Use protective gloves, a lab-coat and safety glasses while handling this compound. Silver(I) oxide is also light sensitive and should be store protected from light.

Dimethyl sulfate (Me_2SO_4)

Dimethyl sulfate is a carcinogenic, mutagenic, highly poisonous, corrosive and volatile liquid. Its vapor has no strong odor or immediate irritation to warn of lethal concentration in the air. Hence, it is essential to store and use this compound only in a well-ventilated area. Dimethyl sulfate is also absorbed through the skin and causes severe skin burns and eye damage. Use of protective gloves, a lab-coat and safety glasses are required when handling dimethyl sulfate.

Methyl iodide (MeI)

Methyl iodide is a volatile liquid exhibiting acute toxicity for inhalation and ingestion and causes eye, skin, and respiratory tract irritation. Furthermore, it can be absorbed through the skin, is suspected of causing cancer and may affect the central nervous system. Only work in a ventilated fume hood and use protective gloves, a lab-coat and safety glasses while handling this compound.

Dilauroyl peroxide

Keep away from heat sources as heating dilauroyl peroxide may cause a fire.

Benzoyl peroxide

Dry benzoyl peroxide is heat, shock and friction sensitive. The resulting decomposition can become violent, releasing large volumes of hot, flammable gasses, resulting in a fire or even an explosion. Keep away from heat sources and store at temperatures not exceeding 30 °C.

Azobisisobutyronitrile (AIBN)

Keep away from heat sources as heating AIBN may cause a fire. It is also a toxic compound and protective gloves, a lab-coat and safety glasses have to be used when working with AIBN.

Tributyltin hydride

Tributyltin hydride is a highly toxic chemical and causes skin irritation on contact. Use protective gloves, a lab-coat and safety glasses while handling this compound.

Aryldiazonium salts

Isolating aryldiazonium compounds requires extra care as the dry solids of the less stable diazonium salts are rather explosive. Only salts of non-nucleophilic anions, such as tetrafluoroborates and hexafluorophosphates, are stable enough to allow isolation and storage. These aryldiazonium salts need to be stored dry and at a low temperature.

Tetrafluoroboric acid (HBF_4)

Tetrafluoroboric acid is a strong, corrosive fuming acid causing severe burns to skin and eyes. Work in a ventilated fume hood and use protective gloves, a lab-coat and safety glasses when handling this compound.

Boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$)

Boron trifluoride diethyl etherate is a colorless, corrosive and flammable liquid causing severe skin burns and eye damage. Its vapor is flammable and toxic by inhalation. Handle this compound in a ventilated fume hood using protective gloves, a lab-coat and safety glasses.

Potassium dichromate ($K_2Cr_2O_7$)

Potassium dichromate is a strong oxidizer, contact with combustible materials may cause a fire and contact with skin causes severe burns. This compound can also cause cancer, impair fertility, cause heritable genetic damage and harm unborn children. Hence, it should always be handled using protective gloves, a lab-coat and safety glasses.

Borane tetrahydrofuran ($BH_3 \cdot THF$)

Borane tetrahydrofuran is a colorless, toxic and highly flammable liquid and was used as a 1.0 M solution in THF. It reacts violently and exothermally with water, moist air, acids, or alcohols liberating flammable hydrogen gas which can ignite explosively. Furthermore, this compound evolves flammable and toxic diborane gas above 50 °C. When handling or using borane tetrahydrofuran, all sources of ignition, such as heat, sparks, or open flame, should be avoided and the compound should be store below 30 °C under a dry nitrogen or argon atmosphere. Also avoid contact with air, humidity and any direct contact with water. Borane tetrahydrofuran can be absorbed through the skin or its vapor can be inhaled resulting in skin and respiratory irritation respectively. Always work in a ventilated fume hood and use protective gloves, a lab-coat and safety glasses when handling this compound.

9-Borabicyclo[3.3.1]nonane (9-BBN)

9-BBN is a flammable solid and was used as a 0.5 M solution in THF. It reacts violently and exothermally with water, moist air, acids, or alcohols liberating flammable hydrogen gas which can ignite explosively. When handling or using 9-BBN, all sources of ignition, such as heat, sparks, or open flame, should be avoided and the compound should be store below 30 °C under a dry nitrogen or argon

atmosphere. Also avoid contact with air, humidity and any direct contact with water. Furthermore this solution can cause skin and respiratory tract irritation. Always work in a ventilated fume hood and use protective gloves, a lab-coat and safety glasses when handling this compound.

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